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Neuroradiological correlates of neuropsychological functioning in multiple sclerosis.

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**Neuroradiological Correlates
of Neuropsychological Functioning in Multiple Sclerosis**

by

Lisa Ann Smith-Walker

B.Sc.(Honours), Queen's University, 1990
M.A., University of Windsor, 1992

A Dissertation
Submitted to the College of Graduate Studies and Research
through the Department of Psychology
in Partial Fulfillment of the Requirements for
the Degree of Doctor of Philosophy at the
University of Windsor

Windsor, Ontario, Canada

1998

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ABSTRACT

The correlation between the pathological changes of multiple sclerosis and the subcortical dementia profile was investigated. The relationship of demyelination (as detected by T2-weighted and gadolinium-enhanced T1-weighted MRI imaging), to both physical disability (as documented using the Expanded Disability Status Scale), and cognitive deterioration (as detected by neuropsychological assessment), was examined. Twelve individuals with early-stage relapsing-remitting MS underwent serial imaging, neurological examination, and neuropsychological assessment at both baseline and 6-month follow-up. Results revealed mild deterioration in functioning with respect to all four aspects of the subcortical dementia profile (i.e., attention and information processing speed, memory, executive functioning, and affective disturbance). Although no significant correlation was found between pathology and ratings of disability, pathology was found to correlate with cognitive functioning. Specifically, total lesion load predicted a significant amount of the variability in attention and executive functioning at baseline and follow-up, and in memory at baseline. Total lesion load was not significantly related to affective disturbance. No significant changes took place over time with respect to pathology, attention, memory, or affect. However, executive functioning improved to a mild degree. The significant relationship between pathology and cognitive dysfunction were discussed in the context of the subcortical dementia profile. The notion of clinically-silent lesions in multiple sclerosis was brought into question. It was recommended that neuropsychological assessment become a standard outcome measurement technique in future clinical trials for multiple sclerosis.

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This project was an adjunct to a larger study being conducted by the MS Clinic of the Ottawa General Hospital, under the supervision of Dr. Mark Freedman. I thank him for the access to the patients, and for the opportunity to be involved in such an interesting

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DEDICATION

This dissertation is dedicated to the individual whose work prompted me to enter the field of Neuropsychology, Dr. Oliver Sacks. Although I have not had the privilege of meeting him personally, his great insight, knowledge, empathic understanding, and most of all, his compassion for his patients, have been inspirational to me.

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CHAPTER 1

MULTIPLE SCLEROSIS

Multiple sclerosis (MS) is characterized by a patchy loss of myelin in the central nervous system. The symptoms are varied and manifest themselves differently in each afflicted individual. An understanding of symptoms and their underlying etiology requires knowledge of MS pathology. This paper will provide a foundation. Pathology will then be discussed in the context of neuroimaging. Recent advances in magnetic resonance imaging (MRI) have provided investigators with new insight into MS. Neuropsychological findings in MS will be discussed in the context of Cummings & Benson's (1984) concept of subcortical dementia. Finally, research which has examined the correlation between pathological findings on MRI and neuropsychological variables will be addressed. This is a new and promising area of research which takes advantage of previously acquired knowledge regarding MS.

Epidemiology of Multiple Sclerosis

MS is a disease with a curious distribution pattern involving distinct geographical areas throughout the world. Practically nonexistent near the equator (Poser, Alter, Sibley & Scheinberg, 1984), MS has a prevalence rate of less than one per 100,000 (Adams & Victor, 1985). As latitude increases in both the northern and southern hemispheres, so does the disease. The rate of MS reaches 30 to 80 cases per 100,000 in North America, Europe, South Australia, and New Zealand (Pearlman & Collins, 1990). The United States has an annual incidence rate of 8,800 cases (McArthur, 1987). Canada reports more cases than the southern United States, where the incidence rates are 30 to 80 as

opposed to 6 to 14 per 100,000 respectively (Adams & Victor, 1985). The highest rates are observed in the Shetland and Orkney Isles (north of Scotland), where the rates are in excess of 150 per 100,000 (Poser et al., 1984). Poser et al. suggest that we should consider the distribution in terms of zones of high, medium and low frequency rather than absolute numbers, because the methods of case finding and diagnostic criteria vary.

The disease is distributed unevenly between sex and race. Women are more susceptible than men by a ratio of about 1.5 to 1 (Poser et al., 1984). MS is also more prevalent in whites than in African-Americans, but geography still plays a role in the distribution pattern of both races (Poser et al., 1984). MS is relatively rare in Asian populations, raising the possibility of a genetic or environmental resistance.

Migratory studies suggest that "persons who migrate from a high-risk to a low-risk zone carry with them at least part of the risk of their country of origin, even though the disease may not become apparent until 20 years after migration" (Adams & Victor, 1985, p. 701). Incidence rates of northern Europeans who immigrated to South Africa were 50 per 100,000, a number only slightly less than their counterparts who remained in Europe. Native born white South Africans demonstrated a rate of 3 to 11 per 100,000. Individuals who immigrated before the age of 15 years demonstrated incidence rates of the South African community to which they immigrated, but those immigrating after the age of 15 demonstrated incidence rates of their native country (Adams & Victor, 1985).

This curious phenomenon has led researchers to speculate as to the cause. Poser et al. (1984) stated that these data have been "interpreted in terms of the acquisition at a critical period of an infectious agent with long latency or conversely, the acquisition prior

to that critical period of some temporarily effective protective, possibly immune mechanism" (p. 601). Immune system involvement will be discussed later with respect to theories of etiology.

MS rates also correlate positively with level of education and measures of good sanitation (Poser et al., 1984). Affluent families possess a higher risk for MS which suggests that their lifestyle may be a causal factor. Poser et al. suggest that families higher in socioeconomic status "consume more animal fat and the association between risk of MS and increased socioeconomic status could support a dietary as well as an infectious cause of the disease" (p. 601).

The role of genetics in MS is controversial. The risk of first degree relatives of MS patients developing the disease is 5 to 15 times greater than the general population (Lynch, Rose, Smoker & Petajan, 1990). Adams and Victor (1985) state that concordance rates between monozygotic and dizygotic twins are not significant, whereas Pearlman and Collins (1990) report that the concordance rate for monozygotic twins is 40% and for dizygotic twins is 1 to 2% (the same as regular sibling pairs). Although a genetic component probably does exist, the lack of complete concordance between monozygotic twins, as well as research on genetic markers, suggests that environmental factors must also be present.

Evidence for environmental involvement has come from studies of the MS "epidemic" in the Faroe Islands (Poser et al., 1984). MS rates increased when the British troops occupied the islands in World War II, and the rates fell after they left. Poser et al. suggest that there "was some evidence that close contact between the bivouac area of the

troops and the residences of the patients may have been a causative factor" (p. 601).

These findings, as well as those of familial concordance rates, correlation with socioeconomic status, and geographic and racial distribution, suggest that MS is neither fully genetically-based nor fully environmentally-based, but rather, seems to be multifactorially determined.

Theories of Multiple Sclerosis Etiology

The exact cause of MS is unknown at the present time. However, two theories have been postulated. The first suggests that MS is caused by the infection of a viral agent (Poser et al., 1984). Viral infection, supposedly occurring in childhood (Lee, Moore, Golenwsky & Raine, 1990), has a long incubation period. This would account for the fact that migrating age (above or below 15 years) plays a critical role in the incidence rates of the disease. According to this theory, environmental factors have an influence on when the disease becomes clinically manifested (Poser et al., 1984). Occasionally, viruses have been isolated from the brains of MS patients, but in the past this has occurred only inconsistently (Poser et al., 1984). Also relevant is that no viral model of MS has been produced experimentally (Adams & Victor, 1985). More recent investigations have suggested that a herpes virus may contribute to the later development of MS (Sanders, Waddell, Felisan, Li, Conrad, & Tourtellotte, 1996).

The second theory proposes a problem with immune regulation (Poser et al., 1984). It is possible that an autoimmune response to myelin occurs as a result of a myelin antigen (Pearlman & Collins, 1990). MS patients have a higher concentration of antibody titers in their CSF for measles virus than do normals. These "elevated titers may imply

greater immune responsiveness or decreased suppression of the immune response to infection" (Poser et al., 1984, p.593). There is also evidence, in the form of increased levels of gamma globulin in the CSF, that suggests that other antibodies may also be elevated. In addition, MS patients show different ratios of T and B cells in their CSF than do normals (Poser et al., 1984).

The two theories are not mutually exclusive. Both viral and immune system mechanisms could play a role, either singly or in interaction with each other. Poser et al. (1984) suggest that:

"Genetically predisposed individuals... may respond to viral infection with altered cellular or humoral immunity or both. Later, the same viral infection or even nonspecific environmental factors... could create the immunoregulatory state that allows an autoimmune attack upon central myelin. Restoration of a balance between immunosuppressor and cytotoxic cells might induce clinical remission" (p.594).

Thus, a combination of both theories seems the most appropriate interpretation at the present time.

Pathology and Neurophysiology of Multiple Sclerosis

The lesions associated with MS are usually not visible on the surface of the brain. Lesions become obvious only after the brain is sectioned. Their size can vary from the size of a pinhead to an area taking up the majority of a hemisphere (Poser et al., 1984). Powell and Lampert (1983) note that the plaques or lesions rarely have a diameter more than 1.5 cm. They may appear larger if many small plaques have coalesced, termed confluent lesions.

The lesions are found particularly in the white matter because MS is a disease

which primarily affects oligodendrocytes and myelin . The lesions, resulting from selective loss of myelin, generally leave the axons of the cells intact; however, more severe lesions may also damage or even destroy the axons as well (Poser et al., 1984). Lesions of the grey matter occur also, and although they are less visible, they are more abundant than those of white matter by a ratio of 4 to 1 (Powell & Lampert, 1983). There is some suggestion that, in addition to the lesions, "normal" white matter in individuals with MS may possess different properties than white matter in individuals who do not have the disease (Lacomis, Osbakken, & Gross, 1986).

Lesions can be found anywhere in the brain and the spinal cord but are most often in the areas closest to spinal fluid pathways (periventricular areas). Although the lesions appear to affect different areas randomly "areas such as the periventricular white matter, periaqueductal grey matter, floor of the fourth ventricle, peripheral cerebral gyri, corpus callosum, optic nerve, and optic chiasma and tracts are particularly affected" (Powell & Lampert, 1983). It is possible that these areas are affected due to their proximity to the CSF which may contain demyelinating factors (Powell & Lampert, 1983). Drayer and Barrett (1984) divide the distribution of lesions into four areas "(a) the optic nerves, chiasm, and tracts, (b) the cerebrum, (c) the brainstem and cerebellum, and (d) the spinal cord" (p. 295). They also note that lesions are often symmetrically distributed.

Powell and Lampert (1983) draw a distinction between "active" and "old" plaques. Active plaques possess indistinct borders with the surrounding tissue due to the collection of many cells and inflammation around the site of demyelination. The role of inflammation in the formation of lesions "remains unclear, some authors regarding it as

secondary to myelin breakdown produced by an independent mechanism... while others consider it to be pathogenetically related to demyelination" (Kermode et al., 1990).

Inflammation is usually perivascular (Nesbit, Forbes, Scheithauer, Okazaki & Rodriguez, 1991). The site of inflammation may appear pink depending on the amount of vascular activity. Also present around the vessels are lymphocytes, macrophages and plasma cells (Powell & Lampert, 1983). These cells allow the debris from the lesion to be phagocytized (Poser et al., 1984). The macrophages break down the myelin and digest it, giving the cells a "foamy" appearance (Powell & Lampert, 1983).

During the period of inflammation, astrocytes proliferate, and then linger after inflammation subsides (Powell & Lampert, 1983). Lee et al. (1990) suggest that in addition to macrophages, astrocytes also play an important role in myelin degradation. A second role played by astrocytes requires them to act "as myelin phagocytes and antigen presenting cells (APC) to T cells" (Lee et al., 1990). The astrocytes signal the T cells that the myelin, which acts as an antigen, should be destroyed. This stimulates antibody production against the body's own tissue.

Because so many glial cells are present around the lesion site, and their presence causes damage in tissue texture, the plaques have acquired the term "sclerosis" (Powell & Lampert, 1983). Sclerosis is a hardening of tissue. The breakdown of myelin in MS does not follow a linear course like that seen in Wallerian degeneration. Instead, one can see myelin in various stages of breakdown throughout the active lesion (Powell & Lampert, 1983). Histological analysis may reveal a plaque which is chronic in appearance in the centre with an active periphery (Nesbit et al., 1991).

The invasion of macrophages in the early stages of an active lesion is thought to be related to the breakdown of the blood-brain barrier (BBB) (Nesbit et al., 1991). Experimental disruption of the BBB has led to a sequence of pathological changes: "initial vasodilation followed by capillary endothelial cell alterations and white matter edema. Venous stasis is then seen associated with the vasodilation followed by a macrophage response and finally perivascular demyelination" (Drayer & Barrett, 1984, p.301). Research has demonstrated that individuals with MS can exhibit perivascular inflammation without accompanying myelin breakdown, leading researchers to conclude "that a vascular event is a necessary preliminary to the development of structural damage" (Kermode et al. 1990, p. 1477). The pathology associated with BBB breakdown can now be visualized using MRI contrast agents (see below).

Old plaques seen in chronic MS, differ from those in the active stage. They are grey rather than pink and distinct from the surrounding tissue. Gliosis causes the grey gelatinous appearance. Since the inflammation seen in the active plaques is no longer present and there is no excess fluid, the old plaque seems more visible (Powell & Lampert, 1983). Although the plaques in the grey matter are more abundant, because of their grey appearance they are more difficult to recognize. These plaques are characterized by nonmyelinated axons, many astrocytic processes and a lack of oligodendroglia. Axons themselves may be less in number, likely a result of Wallerian degeneration (Nesbit et al., 1991). This loss of oligodendroglial cells is a prominent feature of MS (Powell & Lampert, 1983). Despite this situation within the plaque, "the margins of some plaques are hypercellular because of proliferated oligodendrocytes

caused by persistent chronic inflammatory cells" (Powell & Lampert, 1983). Powell and Lampert (1983) also note that the margins of cells demonstrate that some attempts were made at remyelination, which is also a prominent feature of MS.

In addition to "active" and "old" plaques, there are also other lesion sites known as "shadow" plaques, where previously demyelinated axons show some evidence of remyelination. The oligodendroglia adjacent to the axons attempt to provide them with new myelin sheaths. Unfortunately, this myelin demonstrates abnormal characteristics (Powell & Lampert, 1983).

Pathology and disease activity varies with the course of the illness. For example, the lesions in secondary progressive MS patients are generally larger and greater in number than those with primary progressive MS. In addition, patients with benign MS do not have as many confluent periventricular lesions and infratentorial lesions as those with secondary progressive MS. Gadolinium (see below) is not as useful in the imaging of patients with primary progressive MS because very few lesions enhance (Miller, Barkhof, Berry, Kappos, Scotti, & Thompson, 1991).

In addition to the pathological changes concomitant with MS, neurophysiological changes also take place, which generally take the form of disturbances in neuronal conduction of impulses, or action potentials. It is this, that eventually leads to the clinical signs and symptoms. In addition to the lack of myelination, the conduction difficulties are also exacerbated by the inflammation and gliosis occurring in active and old plaques respectively (Eisen, 1983).

There are a number of different manifestations of the conduction problem. The first is *conduction slowing*. This problem leads to clinical symptoms in only a portion of individuals with MS, and can be confirmed by evoked potential studies, in which the rate of conduction can be measured (Eisen, 1983).

Second, conduction problems may also lead to *increased temporal dispersion*. This is the tendency for impulses related closely in time to scatter. It "causes asynchrony of impulse traffic in the variably demyelinated nerve fibres" (Eisen, 1983, p.617), and seems to be more responsible for more clinical symptoms than does simple slowing of impulses.

A third difficulty in MS is *conduction block*, where the impulse does not reach its intended goal. The information carried is blocked from travelling any further. This is the most important conduction problem that MS patients experience (Eisen, 1983). Since the nodes of Ranvier are increased in size when demyelination occurs, this reduces the rate of depolarization. As a result, sodium channel activation thresholds increase. When the threshold becomes too high to reach, conduction is blocked (Eisen, 1983). Sodium channel activation possesses a "safety margin", so that there is usually more than enough activation to permit impulse flow. When activation is lost, the impulse still moves on. With MS, a number of factors can reduce the safety margin, thereby halting conduction. One factor that reduces this safety margin is temperature. As temperature rises, conduction is blocked. This accounts for why MS symptoms are exacerbated after hot baths or strenuous exercise (**Uhthoff's phenomenon**). The higher "temperature shortens the duration of the action potential reducing action currents necessary for sodium channel

activation" (Eisen, 1983, p.617).

Another conduction difficulty is an *inability to transmit trains of impulses*.

Neurons have an increased refractory period and can relay only one action potential. They cannot relay any more stimulation that occurs closely in time to the first. The later impulses are blocked. This phenomenon is also exacerbated by rises in temperature (Eisen, 1983).

In addition to conduction difficulties, MS sufferers also experience **positive** symptoms elicited by hyper-excitability of the axons. This characteristic "may be manifested by spontaneous and mechanosensitive ectopic excitation, autoexcitation, and ephaptic transmission" (Eisen, 1983, p.618). Ectopic excitation is the generation of impulses at sites along the axon other than where they normally originate. This may be responsible for the sensations of electric shock that MS patients often feel travelling down their legs (Lhermitte's sign). This difficulty can occur spontaneously when another impulse in the same fibre occurs (autoexcitation). Ephaptic transmission, also termed "cross-talk", is when information is transferred "from a bare, continuously conducting axon to a myelinated one" (Eisen, 1983, p.618).

Diagnosis of Multiple Sclerosis

In the past, MS was diagnosed solely on clinical criteria. The diagnostic criteria utilized by physicians were usually those of McAlpine (Tedeschi, Allocca, Costanzo, Diano & Bonavita, 1989). Unfortunately, these criteria take into account only clinical and historical findings, and ignore any information obtained from studies in the laboratory. According to these criteria, in order for a patient to be given "a diagnosis of definite MS.

the patient should have a history of two episodes of neurologic symptoms affecting discrete areas of the CNS and should have evidence on examination of white matter involvement in at least one area" (McArthur, 1987, p.141). There are three classifications of diagnosis: 1) clinically definite MS, 2) probable MS, and 3) possible MS (Poser et al., 1984). Appendix A lists the criteria for inclusion in each of these categories. The requirements for definite MS, outlined by Poser et al. (1984), delineate that the patient must be experiencing symptoms in a relapsing and remitting course, such that two symptomatic periods are separated by at least one month, or else the disease must demonstrate a slow progressive course for at least 6 months. This symptomatology, which must appear between the ages of 10 to 50 years, must not be accounted for by any other neurological explanation (Poser et al., 1984). These criteria do not take into account any of the information that can be supplied by laboratory or neuroradiological measures.

Two laboratory methods proven useful in MS diagnosis are 1) evoked potentials, and 2) CSF analysis. Both methods were studied by Bartel, Markand & Kolar (1983) in order to assess whether they were sensitive to the physiological changes associated with MS. They divided MS patients into the three diagnostic categories discussed above, and obtained several evoked potential measures (i.e. brainstem auditory evoked responses [BAER], visual evoked responses [VER], and somatosensory evoked responses [SER], as well as a CSF analysis). At least one abnormal evoked response [ER] was found in 75% of all subjects, with the definite MS group demonstrating the highest incidence. When each ER was analyzed separately, all were found to show the greatest abnormality in the definite MS group. Predictive value was greatest when all three ERs were entered into the

analysis. Although all three types yielded the most accurate results, it was found that of the three, SERs were more sensitive than either VERs or BAERs. The analysis of CSF yielded abnormalities in 68% of all MS patients, again with the highest incidence of abnormality occurring in the definite MS group. The results also suggested that the probability of CSF abnormality increased when ERs were also abnormal.

Thus, the abnormalities found in ERs and CSF are potent predictors of MS. Bartel et al. (1983) suggest that this information would be a valuable addition to the current criteria used to diagnose MS. They propose that the new criteria should read as follows:

"(1) history of neurologic symptoms with relapses and remission, (2) evidence of two or more anatomically separated lesions in the CNS obtained by clinical examination, electrophysiologic tests, or both, and (3) evidence of immunologic disturbance involving primarily the CNS, revealed by a demyelinating CSF profile" (p. 616).

They believed that the inclusion of these new criteria would yield greater strength to the clinical diagnostic strategy already in use, and might also allow for the detection of the disease earlier in its course.

In 1982, several researchers and clinicians took part in a workshop in Washington D.C. in order to establish diagnostic criteria which would take advantage of recent advances in technology. Poser and his colleagues published the results of their efforts, and at present his name is synonymous with these criteria (Poser et al., 1983).

Essentially, patients are classified into one of 2 major categories: definite MS and probable MS. In turn, these classifications are further subdivided into clinical and laboratory-supported. In order to assign patients to a category, one must consider the following: the number of attacks (neurological dysfunction lasting more than 24 hours).

clinical evidence (as demonstrated through a neurological exam), paraclinical evidence (i.e., hot bath test, evoked response study, tissue imaging, urologic assessment), and CSF analysis. See Appendix B for an outline of these criteria.

Several authors have examined the diagnostic utility of other, less common, laboratory techniques. A number of studies examine properties of the visual system in MS patients. The visual system is particularly vulnerable to insult in MS because lesions are often found in the optic tracts or chiasm. Often, upon autopsy, lesions are found in the visual system that were clinically silent. The frequency of these findings has approached 100% (Menabue, Nichelli & Bellei, 1986). It would therefore seem appropriate to devise tests which would pick up behavioural anomalies associated with these lesions, and to use this new found information for more reliable diagnosis. For instance, Menabue et al. (1986) demonstrated that a tachistoscopic test of colour discrimination yielded poorer performance of MS patients when compared to controls.

The utility of the assessment of saccadic eye movements (SAM) as a diagnostic tool has also been demonstrated. Tedeschi et al., (1989) examined the diagnostic utility of SAM compared with that of MRI scans. MS subjects were separated into three categories: definite, probable, and possible. MRI was a more sensitive predictor of definite MS, whereas the SAM assessment was more sensitive for the probable and possible groups. The authors suggest that evaluation of SAMs is important since MRIs do not allow physicians good visualization of areas such as the brainstem and medial longitudinal fasciculus. The SAM test would pick up difficulties arising from lesions in these areas (Tedeschi et al., 1989). Meienberg, Muri and Rabineau (1986) also observed saccadic

eye movements in MS patients in order to assess the diagnostic value. Results revealed that about one third of the definite and possible MS patients in their study demonstrated saccadic abnormalities.

One last test to be mentioned that might possibly aid in diagnosis is the assessment of hair follicle discrimination (Schneider & Burke, 1982). This is a test of somatosensory functioning which asks the subject to detect whether a leg hair was displaced to 9.45 mm or to 6.20 mm. The MS patients were separated into those who demonstrated sensory symptoms and those who did not. MS patients with sensory problems were poorer at discrimination of the stimulus than were MS patients without sensory symptoms, and normal controls. Although this method distinguishes between patients *within* the MS population, this method does not possess good diagnostic utility as it predicts only a subset of MS patients.

This brief review of diagnostic tools has revealed a number of different possibilities for assessment. Clinical symptoms and history are still used as the primary method of diagnosis; however, in terms of secondary assessment techniques, the methods of choice are evoked responses and CSF analysis. At present, most researchers try to adhere to Poser's diagnostic criteria.

The Clinical Course of MS

Although variable, the onset of MS symptomatology is usually acute or subacute, such that symptoms occur relatively suddenly (Poser et al., 1984). Despite individual differences, some symptoms and signs appear frequently at onset. An initial presumptive diagnosis can be arrived at by observing the pattern of symptoms (Poser et al., 1984).

Sometimes a detailed review of the patient's history reveals that the patient has experienced symptoms in the past, but they were ignored or interpreted as being caused by something else. Poser et al. (1984) stated that: "this is particularly true of transient paresthesias, mild urinary disturbances (often erroneously diagnosed and treated as painless urinary tract infections), and mild ocular manifestations such as blurring of vision or transient diminution of monocular activity" (p. 605). The most common symptoms of MS that appear at onset are muscle weakness, ocular and cerebellar disorders, and paresthesias (Poser et al., 1984).

Sometimes patients will present with spinal cord or brainstem lesions. Miller, Ormerod, Rudge, Kendall, Moseley and McDonald (1989) studied these individuals on follow-up in order to see what percentage would later progress to definite MS. Fifty-seven percent of their patients with brainstem syndrome and 42% with spinal cord syndrome, progressed to MS. The mean interval between symptom onset and MS diagnosis was 15-16 months. They stated that:

"the risk of progression was increased by the presence of oligoclonal bands in the cerebrospinal fluid of patients with either syndrome and by the presence of disseminated brain lesions, as detected by magnetic resonance imaging, in those with a spinal cord syndrome" (Miller et al., 1989, p. 635).

This information may aid in the earlier diagnosis of the disease, or at the very least, may give patients an opportunity to know they are at risk.

The course of MS is also variable. People may demonstrate the biological changes associated with MS in the form of lesions, but these lesions may never express themselves clinically. An important question is raised here: can we say that people with these clinically silent lesions really possess the disease?

Adams and Victor (1985) stated that "the disease advancing in a series of attacks each permitting less and less remission, is one of the most important clinical attributes of the disease" (p. 708). Although this may be the case in general terms, Poser et al. (1984) suggested that individuals with MS fit into one of four categories: benign, exacerbation-remitting, chronic-relapsing, and chronic-progressive. The descriptions given to each are as follows. The benign group, which represents 20% of the MS population, is characterized by mild exacerbations of symptoms early in the course of the disease, but they demonstrate total or near total remissions. This group does not demonstrate anything beyond a minimal disability. The exacerbation-remitting group (labelled by others as relapsing-remitting), which represents 25% of the MS population, are similar to the benign group in that they demonstrate early exacerbations. The difference is that the remissions are not total. Despite their symptoms, this group has some disability, but they also experience long periods where their condition is stable. The chronic-relapsing group represents 40% of the MS population. This group demonstrates "fewer remissions as the disease progresses and increasing (cumulative) disability" (Poser et al., 1984). Lastly, the chronic-progressive group, representing 15% of the MS population, is the most disabled subgroup. They demonstrate a steady decline with symptoms progressing from the time of onset.

There is a general rule that clinicians use to help them in providing patients with a prognosis. Poser et al. (1984) suggested that "sensory symptoms at onset (e.g., blurred vision, or paresthesias) tend to indicate a benign course, whereas early cerebellar and corticospinal signs imply a chronic-relapsing or chronic-progressive course" (Poser et al.,

1984, p. 608).

Adams and Victor (1985) stated that the duration of the disease is variable. "A small number of patients die within several months or years of the onset, but the average duration is in excess of 30 years" (p. 708). MS is not usually the primary cause of death. Rather, it is usually due to some secondary infection, such as a urinary tract infection, respiratory tract infection, or decubitus ulcer (Poser et al., 1984).

Symptomatology

A great variety of symptoms are possible manifestations of this disease. The type of symptoms that each individual patient experiences is dependent upon the site of the lesions in their CNS. Therefore, it is logical that a discussion of the symptoms should categorize each according to its anatomic locus.

Reder and Antel (1983) exercised this type of classification of symptoms according to the following lesion sites: spinal cord, cerebellum and its efferent pathways, brain stem, optic and olfactory nerves, and the cortex.

As noted previously, patients experiencing spinal cord syndrome often progress to MS (Miller et al., 1989). Reder and Antel (1983) note that most of the motor and sensory disturbances experienced by MS patients are a result of lesions in the spinal cord. The corticospinal tract and ascending sensory pathways are here, so these too can be affected. A number of symptoms can occur, so each will be listed here rather than discussed in detail (Reder and Antel, 1983, p. 575):

- fatigue; low endurance for physical activity
- heaviness, stiffness, or weakness of limbs
- tripping and stumbling while walking

- hyperreflexia and spasticity
- amyotrophy (degeneration of motor neurons)
- recurrent and painful tonic spasms of the limbs
- Lhermitte's sign (electric shock sensation down back with neck flexion)
- pain mimicking muscle or joint aches
- painful dysesthesias
- disruption of vibration and position sensations
- constipation
- urinary bladder and sexual dysfunction
- acute transverse myelitis (inflammation of spinal cord)

The symptoms resulting from spinal cord lesions more often affect the lower extremities. In fact, the legs are affected twice as frequently as the arms (Reder & Antel, 1983). Reder and Antel (1983) suggest that this is because the corticospinal tracts which supply the legs are of greater length than their counterparts for the arms. The legs therefore have a greater chance of being affected by lesions than do the arms just by sheer volume. The same situation is found in the case of cerebellar (and its efferent pathways) symptoms, where the legs are more often affected (Reder & Antel, 1983). Approximately 50% of MS patients exhibit symptoms resulting from cerebellar lesions. Unfortunately, these symptoms can be quite disabling. The patient may experience intention tremors of the limbs, and titubation (shaking) of the trunk. Balance and speech may also be affected, such that the patient may have trouble walking and standing, and they may experience dysarthria.

MS lesions may also affect the functions of the brainstem. This is particularly noted in the facial region due to the involvement of the cranial nerves. The following are some symptoms that may be experienced by patients with brainstem lesions (Reder & Antel, 1983, p. 576):

- diplopia (double vision)
- facial paresthesias or loss of sensation
- trigeminal neuralgia (stablike pain in the jaw area)
- facial weakness (mimics Bell's palsy)
- hearing loss
- vertigo
- nystagmus
- hypersomnia
- polyphagia (eating to the point of gluttony)

Reder and Antel (1983) also report symptoms associated with the optic nerve.

They note that optic neuritis (inflammation of the optic nerve) occurs in 25 to 40% of MS patients. The development of this particular symptom appears to be over a period of a few hours to a few days. The symptoms, which may be intense (complete blindness) or minor (reduced depth perception with moving objects), usually lessen or disappear over a period of a few weeks (Reder & Antel, 1983). As mentioned in the previous paper, optic symptoms may be present in up to 100 percent of MS patients (as observed upon autopsy). Although Reder and Antel (1983) only report the symptoms in up to 40% of patients, more subclinical difficulties may be revealed through visual evoked procedures.

Finally, the higher cortical functions of MS patients may also be affected. It is these lesions in the cortex, causing neuropsychological deficits, that might lead an MS patient to a neuropsychologist. Reder and Antel (1983, p. 577-8) report the following symptoms resulting from cortical lesions:

- dementia (especially uncommon in early stages)
- seizures
- mood changes (euphoria, depression)
- aphasia
- cortical deafness

The time at which the symptom develops in the course of the illness is also

significant. Some symptoms are more likely to be present during the beginning stages of the disease, while others are more likely in the latter stages. In the early stages of MS, 50% of patients are likely to complain of limb weakness and/or numbness. The patient may only experience symptoms in one side of the body, when in fact, upon examination, they may exhibit bilateral corticospinal and posterior column disease (Adams & Victor, 1985). Another symptom often presenting first is acute optic neuritis. This occurs first in approximately 25% of patients (Adams & Victor, 1985). A combination of symptoms that presents initially only rarely, is known as **Charcot's triad**. This consists of nystagmus, scanning speech, and intention tremor. These symptoms indicate involvement of cerebellar and corticospinal tracts (Adams & Victor, 1985).

Whether or not the symptoms appear quickly, has an effect on how long they are present. Bannister (1985) stated that if "the onset is acute or subacute, the tendency is for the initial symptoms to diminish over a period of weeks or months, and either to disappear completely or to leave behind some residual disability" (p. 510). If the onset of symptoms is more insidious, then the possibility of remission is less evident.

The last stages of the disease are much more bleak. As MS is a progressive disease, at the end of the illness the symptoms are more exaggerated and the individual is much more compromised and handicapped. Bannister (1985) describes the symptoms present in the advanced stages of MS:

"the patients will be bedridden with scanning or staccato speech and slurring of individual syllables, pallor of both optic discs, nystagmus, and a dissociation of conjugate lateral movement of the eyes, the abducting eye moving outwards further than the adducting eye moves inwards. The upper limbs will be weak and grossly ataxic. There will be severe paraplegia,

either in extension interrupted by flexor spasms, or in flexion. Cutaneous or deep sensory loss, or both, may be present in upper and lower limbs, and there is likely to be incontinence of urine and faeces" (p. 510).

Reder and Antel (1983) listed a number of factors that may have an influence on the course of the illness, and exacerbate symptoms already present. As mentioned earlier, increases in temperature are deleterious to symptoms, and may also bring out new symptoms (Uhthoff's sign). Pregnancy, and the first three months after birth may also exacerbate symptoms. In fact, pregnancy may cause MS to appear earlier in individuals who were already predisposed to the disease. Allergies, spinal anesthesia and stress may also contribute to worsened symptoms.

Despite all of these debilitating symptoms, a surprising proportion of MS patients have been shown to demonstrate a positive attitude towards the disease. Robinson (1990) undertook a large scale examination of the personal narratives and social histories as reported by 50 MS patients. In his analysis he noted that "Narratives which embody an apparently positive and optimistic approach to the presence of the disease... seem particularly - indeed unusually - common" (Robinson, 1990, p. 1181). Although this result seems encouraging, one must be careful in its interpretation as one manifestation of MS is a tendency to deny deficits, or present with a lack of awareness of such. Therefore, this "positive" outlook may be due in part to the fact that the individuals interviewed are simply unaware of the extent of their disabilities and thus are not bothered by them.

CHAPTER 2

MAGNETIC RESONANCE IMAGING

Technology

The advent of more sophisticated imaging techniques, such as magnetic resonance imaging (MRI), has led to the most recent advances in the diagnosis and monitoring of MS. MRI is a reliable method of detecting areas of demyelination (Stewart, Hall, Berry, & Paty, 1984). A review of the technology associated with this neuroradiological technique is necessary in order to further understand how it allows clinicians and researchers alike to gain insight into the disease process. MRI relies upon the physical principle that the tissues in the brain all contain hydrogen, the nuclei of which possess different densities and velocities depending on the tissue type. Thus, one can see the difference between grey and white matter. Further, abnormal changes in the brain (i.e., tumours, demyelination) also possess different hydrogen densities, thus permitting visualization of these differences (Lukes, Crooks, Aminoff, Kaufman, Panitch, Mills, & Norman, 1983).

Lukes et al. (1983) described the physics behind this technology. Hydrogen nuclei possess magnetic properties. Magnetic dipoles are created when these nuclei spin on their axes. The dipoles can become aligned to form a net magnetic vector when placed in a strong magnetic field, such as that created by the MRI machine. In simpler terms, the nuclei will tend to "wobble" about the axis of the externally-applied magnetic field. The vector is thus considered to be parallel to the magnetic field. The vector becomes displaced when a radiofrequency (RF) pulse is applied that is the same frequency as the

"wobbling" of the nuclei. Thus, the nuclei are, in a sense, tilted out of alignment so that they begin to wobble at a higher energy state (Francis, Evans, & Arnold, 1995). The amount of displacement is determined by the strength and duration of the pulse, which is in turn, determined by the strength of the magnetic field (resonant frequency). At the end of the pulse the nuclei will return to their original orientation, thereby emitting a RF signal. The time it takes to return to their original orientation is known as the relaxation time. In order to determine the position of the nuclei in the brain, a gradient is introduced into the magnetic field. An image is then generated from this information (Lukes et al., 1983).

Researchers have demonstrated that there may be no difference between field strengths of 0.5 and 1.5 T with respect to diagnostic utility (Lee, Vellet, Eliasziw, Vidito, Ebers, Rice, Hewett, & Dunlavy, 1995). But varying pulse sequence can effect contrast resolution. Lukes et al. (1983) assessed the contrast resolution of varying pulse intervals (0.5, 1.0, and 1.5 seconds) in their study of 10 MS patients. Contrast resolution was greatest at 1.5 seconds, and more lesions were detected. However, as the pulse interval increases, the potential for motion artifact also increases (i.e., the patient is more likely to move and disrupt the image).

There are two types of relaxation times that can be recorded, each of which generates a different type of image. T1-weighted images, with what is known as the spin-lattice relaxation time, "reflects the interaction of the hydrogen nucleus with its molecular environment," (Lukes et al., 1983, p.592) and T2-weighted images, with the spin-spin relaxation time, "reflects magnetic interactions between nuclei" (Lukes et al., 1983,

p.593). T1 relaxation times (100-1500 msec) are generally longer than T2 relaxation times (10-100 msec) (Buonanno, Kistler, Lehigh, Noseworthy, New, & Brady, 1983). The physics of these two image types is beyond the current discussion; however, it is important to understand that each type has different uses, and that MS pathology (demyelination) appears different on the film with each technique. The inversion recovery method of MRI relies upon T1 images and is the better of the two at differentiating between normal grey and white matter (Lukes et al., 1983). However, the spin-echo method using T2 images "showed many more lesions, especially those situated more peripherally at the grey-white matter junction" (Li, Mayo, Fache, Robertson, Paty, & Genton, 1984, p.483). On T1 images the white matter appears bright against the dark grey matter. MS plaques, or other pathological abnormalities, appear hypointense, or as varying shades of grey. On T2 images white matter appears dark against the lighter grey matter, and lesions are hyperintense, or bright (Lukes et al., 1983). It is generally accepted that T2 images are superior to T1 images in the visualization of the demyelination characteristic of MS. Lukes et al. (1983) found that the T2, or spin-echo, method held two advantages over the T1, or inversion recovery method. "First, the increased signal intensity of involved areas facilitated the differentiation of lesions from adjacent ventricles. Second, a number of areas that appeared normal on inversion recovery images were clearly abnormal on spin-echo images" (Lukes et al., 1983, p.597).

Limitations of MRI and Appearance of Lesions

Although MS plaques can be more readily delineated using MRI technology, these areas of demyelination cannot be easily differentiated from other types of CNS pathology.

Indeed, when multiple lesions are found on an MRI scan this cannot be considered to be pathognomonic of MS (Gerard & Weisberg, 1986; Ormerod, Roberts, DuBoulay, McDonald, Callanan, Halliday, Johnson, Kendall, Logsdail, Macmanus, Moseley, Ron, Rudge, Zilkha, 1984). Several differential diagnoses exist:

"white matter ischemia/infarction; "normal" aging; vasculitis; moyamoya disease; radiation injury; migraine; acute disseminated encephalomyelitis; subacute sclerosing panencephalitis; brucellosis; borreliosis; viral encephalitis; AIDS; granulomatous diseases such as sarcoidosis and tuberculosis; and autoimmune diseases including systemic lupus erythematosus, Sjogren syndrome, and Behcet syndrome. Other demyelinating or dysmyelinating diseases... must also be considered" (Wallace, Seland, & Fong, 1992, p.850-1).

However, the use of substances such as gadolinium, which enhance some lesions (see below), can increase the specificity of MRI in the diagnosis of MS (Tas, Barkhol, van Walderveen, Polman, Hommes, & Valk, 1995).

Additional limitations of the use of MRI to detect MS pathology are as follows: the equipment itself is costly and requires a host site which will allow for a high field strength magnet, the scanning time is longer than that of CT, the possibility of motion artifact makes it more difficult to test very ill or uncooperative patients (Drayer & Barrett, 1984), and the MRI may overestimate the size of the area of demyelination as inflammation and edema associated with active lesions may produce similar signals (Francis et al., 1995).

Despite the extensive list of differential diagnoses, there are findings which are considered prototypical of MS. The lesions are usually (but not always) small (less than 2.5 cm long), and have irregular outlines. Although they may be homogeneous they may

also exhibit a rim of T2 hyperintensity or T1 hypointensity. The lesions are most often perivascular and some may appear "ovoid and perpendicular to the long axis of the brain and lateral ventricles" (Wallace et al., 1992, p.850). Francis et al., (1995) note that "lesions are found predominantly in white matter, particularly in the centrum semiovale or adjacent to the ventricles but are seen less frequently in the posterior fossa... than in the cerebrum" (p.151). If lesions are found in the cerebellar peduncle, cerebellar hemisphere, midbrain or adjoining the fourth ventricle then this is considered as relatively specific for MS (Francis et al., 1995). MRI evaluations have also been useful at providing information regarding the pathological characteristics of various forms of MS. Different clinical courses yield different MRI profiles (Koopmans, Li, Grochowski, Cutler, & Paty, 1989).

Recent advances in the field of MRI (e.g., proton chemical shift, magnetization transfer imaging, diffusion imaging, proton magnetic resonance spectroscopy) suggest that in the future, it may be possible to distinguish between MS and various other forms of pathology (and thus distinguish between disease processes) by measuring variables apart from relaxation time (Miller, 1994; Pykett & Rosen, 1983). For example, recent research with magnetization transfer provides more information about the process of demyelination, where it occurs centrifugally (i.e., myelin loss takes place centrally and then extends peripherally) (Hiehle, Grossman, Ramer, Gonzalez-Scarano, & Cohen, 1995). Three-dimensional imaging techniques allow for greater anatomical precision (Cline, Lorensen, Kikinis, & Jolesz, 1990).

Although MRI depicts MS lesions more readily than CT, it remains an

approximation of actual pathology. Lukes et al. (1983) list several reasons why this is so. First, it is possible that MRI technology detects only specific types of MS lesions (e.g., only those with a specific pattern of edema). Second, comparison between individuals with large areas of confluent lesions and those with many small anatomically distinct lesions is difficult. Third, when lesions are side-by-side, it is difficult to determine their respective boundaries. Last, the thickness of the sections chosen, and the angle at which they are taken, may influence whether or not lesions are detected.

Gadolinium Enhancement

Relatively recent advances in MRI technology allow the differentiation of "old" from "active" MS lesions. For a more detailed discussion of these lesion types see the Pathology and Neurophysiology section of this document. In the past, both T1 and T2 imaging highlighted only the older, more chronic, lesions, but these methods have been relatively insensitive to active, or newer, lesions. The latter can be responsible for the "flare-ups" characteristic of relapsing-remitting MS, although many have been demonstrated to be "clinically silent." The injection into the patient of paramagnetic compounds such as Gd-DTPA (gadolinium diethylenetriamine penta-acetic acid; hereafter referred to as gadolinium) results in these active lesions appearing hyperintense on T1-weighted images due to an increase in the T1 relaxation time, and thus allow for a glimpse at processes that are actually occurring at the time of the scan (Drayer & Barrett, 1984; Francis et al., 1995; Rudick, 1992).

The sensitivity of gadolinium in detecting active disease activity was first established by Miller, Barkhof, and Nauta (1993). Results revealed that gadolinium

enhanced T1 weighted scans were more sensitive than T2 weighted scans at detecting active lesions.

In a follow-up study, Miller (1994) proposed five lines of evidence that gadolinium enhancement is a good indicator of disease activity. First, enhancement occurs more frequently when scans are obtained during clinical relapses. Second, enhancement occurs frequently when lesions first appear in both relapsing-remitting and secondary progressive MS. Third, enhancement generally lasts 2-6 weeks (see below) and thus, corresponds to the duration of clinical symptoms during relapse. Fourth, enhancement correlates with perivascular inflammation in both MS and in experimental allergic encephalomyelitis (an experimental model of MS). Last, the period of visual loss and conduction block seen in optic neuritis corresponds to the period of gadolinium enhancement.

A strong correlation between enhanced lesions on MRI scans and histological data has been established (Nesbit, et al., 1991). Gadolinium crosses from the bloodstream into the brain only at points of blood-brain barrier (BBB) breakdown. Thus, this type of imaging will highlight those lesions that are acute as well as those that are older and have been reactivated. Drug treatment with corticosteroids may restore the BBB and help reduce clinical symptoms, thus in turn will reduce the amount of gadolinium enhancement seen on an MRI scan (Francis et al., 1995). The pattern of gadolinium enhancement has provided researchers with insights into the process of demyelination which are consistent with the findings using magnetization transfer techniques, as noted

above. Specifically, new lesions will appear hyperintense in the centre. As the lesions age, the area of enhancement appears as a ring around a darker central region, thus indicating that demyelination begins centrally and extends peripherally (Guttman, Ahn, Hsu, Kikinis, & Jolesz, 1995).

Opinions differ regarding the period of time that lesions will enhance with gadolinium. Some authors suggest that lesions will be hyperintense for 2 to 4 weeks (Francis et al., 1995), whereas others suggest that enhancement can potentially last beyond 12 weeks. There has been some suggestion that the size of the lesion may impact on the enhancement time, where larger lesions may enhance for a longer period of time (Thompson et al., 1992). Nonetheless, acute plaques can be differentiated from chronic plaques for only this period of time. This short time span emphasizes the fact that pathological changes are taking place rapidly in the brains of individuals with MS, and thus, has implications for research purposes. If researchers are attempting to correlate MRI variables with clinical findings, both radiological and clinical testing should be completed within days of each other. There has been some suggestion that the changes seen in active plaques pre-date clinical symptomatology (Francis et al., 1995).

Miller et al., (1991) list three reasons why gadolinium enhancement is useful with MS patients. First, older lesions may be reactivated and show areas of enhancement, thus, allowing clinicians a more accurate picture of current disease activity. Second, lesions in the cortex and subcortical white matter are more readily observed with gadolinium enhanced scans (as opposed to T2). Third, lesions that may be too small to be considered significant on T2 will become more conspicuous with gadolinium

enhancement.

Side effects from the injection of gadolinium are rare. Miller et al., (1991) reported that anaphylactoid reactions occur with a frequency of about one in 100,000, and no deaths have occurred. However, they do not recommend the use of gadolinium in pregnant women.

MRI versus CT

Although computerized tomography (CT) machines themselves are more convenient for both patients and hospitals, MRI has been demonstrated to be superior to CT scanning with respect to its ability to more accurately delineate the pathology associated with MS (Grossman, Gonzalez-Scarano, Atlas, Galetta, & Silberberg, 1986). This is primarily because MRI scans will demonstrate all lesions seen on CT as well as other lesions that were not observed (Lukes et al., 1983). For instance, Buonanno et al. (1983) found 8 lesions total in 7 patients using CT, but found over 60 lesions in the same patients using MRI. Similarly, a different study of 10 MS patients noted 19 lesions on CT and 112 further lesions on MRI (Young, Hall, Pallis, Legg, Bydder, Steiner, 1981).

Although the ability of CT to detect lesions is enhanced with the infusion of iodinated contrast agents, results remain unsatisfactory. Francis et al. (1995) state that even during acute relapses when disease activity is surely taking place "with the infusion of a double dose of contrast and delayed scanning, only 54% of the scans in such patients show plaques" (p.148). MRI is particularly well suited to detecting small lesions. In their study of 10 MS patients Young et al. (1981) demonstrated that CT was able to detect

lesions 7 mm in diameter and above, whereas MRI could detect lesions as small as 4 mm.

MRI is also superior to CT in its ability to image the posterior fossa. When this area is imaged with a CT scanner there are problems with bony artifact (Francis et al., 1995). In addition, Drayer and Barrett (1984) noted that MRI has better contrast sensitivity, and more easily yields direct sagittal and coronal images.

Monitoring of Disease Progression and Clinical Trials

In the past, disease activity was monitored by clinical data. A patient would experience a clinical exacerbation of symptoms and would undergo a neurological exam. The severity of their symptoms could be documented using a rating scale such as Kurtzke's Expanded Disability Status Scale (Kurtzke, 1983). Although this procedure continues to provide valuable information, MRI studies have demonstrated that symptom exacerbation is not always a good indicator of disease activity. Indeed, several lesions are often observed radiologically which do not correspond to any physical symptoms or clinical relapses (Capra, Marciano, Vignolo Chiesa, Gasparotti, 1992; Isaac et al., 1988; Paty et al., 1994; Willoughby, Grochowski, Li, Oger, Kastrukoff, & Paty, 1989). McDonald, Miller, and Thompson (1994) reported that MRI is 5 to 10 times better than clinical relapse at predicting new pathological activity. Lesions that are not associated with clinical signs are considered to be "clinically silent." Baum, Nehrig, Schorner, and Girke (1990) performed a long-term follow-up of MS disease activity utilizing both clinical assessment and MRI. In a full one third of the 51 patients, disease activity detected on MRI did not correspond to clinical progression. The authors concluded that "a stable clinical status does not necessarily mean the lack of florid inflammatory

activity" (Baum et al., 1990, p.194). Similarly, Truyen, Gheuens, Parizel, Van de Vyver, and Martin (1991) detected disease activity on MRI in 56% of patients who were clinically stable during the follow-up period (mean follow-up 22 months). Miller (1994) reported that "in secondary progressive or early relapsing-remitting MS, new lesions develop on average 5 to 10 times more often on monthly brain MRI than the occurrence of clinical relapses" (p.591-2). References here to clinical relapses are with respect to those detected by standard neurological exam.

MRI has also provided clarification regarding the clinical course of relapsing-remitting (RR) versus chronic progressive (CP) MS. For instance, in the past, some believed that the CP and RR phases of MS were the result of different mechanisms. Serial MRI monitoring of disease activity has demonstrated that this is not the case. Although patients with CPMS had more confluent lesions, "new and changing lesions were indistinguishable in appearance, distribution, and temporal pattern from those previously seen in patients who had relapsing and remitting multiple sclerosis" (Koopmans, Li, Oger, Kastrukoff, Jardine, Costley, Hall, Grochowski, & Paty, 1989, p. 248). Thus, MRI has yielded evidence that cannot be obtained from clinical data.

These findings have implications for clinical trials. In order to monitor the course of illness or evaluate various treatment effects, serial MRI provides a more valid measure of disease activity than standard neurological exam. The use of gadolinium enhanced scans would seem to be the most appropriate choice for lesion analysis since active lesions are the most relevant indicator of current histological change. Not only is gadolinium more reliable than un-enhanced methods, but its use allows for greater

sensitivity such that smaller lesions (that would have been insignificant on un-enhanced scans) are detected (Miller, 1994). Indeed, several authors have already instigated serial gadolinium scanning in their clinical trials with some success (Bastianello, Pozzilli, D'Andrea, Milleriorini, Trojano, Morino, Gasperini, Bozzao, Gallucci, Andreula, Bozzao, Gambi, & Prencipe, 1994; Krapf, Mauch, Fetzer, Laufen, & Kornhuber, 1995; Stone, Frank, Albert, Bash, Smith, Maloni, & McFarland, 1995).

An attempt was made to provide investigators with guidelines for clinical trials in order to ensure uniformity of method between centres. Miller, et al., (1991) report the recommendations derived from a workshop on "The monitoring of MS by magnetic resonance" under the auspices of the Commission of the European Communities (CEC) at a meeting held in London, England in November 1990. The following is a brief outline of their recommendations.

First, one must consider the MRI system itself. A minimum field strength of 0.5 T, with a slice thickness of 5 mm was felt appropriate. The consistent positioning of the patient within the machine is paramount. If multicentre trials are taking place, each centre should agree upon a method of anatomical alignment. When unenhanced techniques are used, T2 was considered to be superior to T1. Gadolinium enhancement was recommended as the method of choice, where scanning should take place 5 minutes post-injection.

Second, care should be taken in selecting patients for inclusion in clinical trials. It is best to utilize patients who exhibit either a relapsing-remitting, or a secondary progressive course (i.e., progressive after a series of relapses) given that they have the

most asymptomatic disease activity.

Third, care should be taken when designing the trial. Clinical assessments and the recording of relapses should be done along with the serial scanning, and the concurrent use of steroid medication should be recorded (given its effect on lesion enhancement). Scans should take place at monthly intervals (in order to ensure detection of all new lesion activity), and should extend for a period of at least 6 months (so that a treatment effect will more likely be shown). Patient compliance may become sporadic if the trial is extended further. Smaller numbers of patients can be used if they are used as their own controls by obtaining MRI images before the treatment period (i.e., a baseline).

Fourth, when analyzing results, hard copies with reasonably large images should be utilized, although storage on tape or disc is recommended. A "phantom" or prototype scan demonstrating lesion appearance may contribute to uniformity between centres. Record should be made of all new enlarging or enhancing lesions. To ensure reliability two experienced neuroradiologists at one centre should be engaged to analyze all scans in a multicentre trial. With respect to quantification of lesions, total lesion area/volume is felt to be inappropriate given that this value fluctuates with time as lesions wax and wane in size, and given that this value is often so small over a short period of time that it falls within the margin of error. Unfortunately, the authors do not recommend an alternative method of quantification.

Correlations Between MRI and Clinical Variables

Given that MRI investigations have proven useful at detecting disease activity, several investigators have attempted to correlate the pathological findings noted on MRI

with various clinical indicators of disease. However, success has been limited. Early studies attempting to demonstrate this link were restricted by technological limitations. For example, three studies conducted in the late 1980's utilized a MRI machine with only 0.15T field strength (Jacobs, Kinkel, Polachini, & Kinkel, 1986; Reese, Carr, Nicholson, & Lepp, 1986; Stevens, Farlow, Edwards, & Yu, 1986). As discussed above, Miller et al. (1991) recommended a minimum field strength of 0.5T. In one case, technological advances were being made during the course of the study itself, so some patients were tested with one set of MRI hardware and software, and other patients were tested with different combinations (Reese et al., 1986). Nonetheless, some small correlations were noted. Stevens et al. (1986) found significant (though modest) correlations between pathology documented on MRI and two disability rating scales (i.e., Kurtzke's Expanded Disability Status Scale [EDSS], Sipe's neurologic rating scale [NRS]). Although the authors measured both number and size of lesions, as well as degree of atrophic change, they did not indicate which variable(s) correlated with the clinical measures. They also failed to report how close in time the clinical neurological examination and the MRI were completed. The latter oversight was also made by Reese et al. (1986). Although these authors found that MRI was better than CT at diagnosis of MS, MRI variables correlated poorly with the EDSS and disease duration. Similarly, Jacobs et al. (1986) demonstrated that MRI was better at detecting lesions than CT, but that only 5% of the lesions documented on MRI correlated with symptoms noted clinically. These lesions were located in the brainstem or cerebellar peduncles.

Several reasons have been postulated to account for this lack of correlation

between pathology and clinical disease activity. These are related to limitations of both MRI and the clinical examinations. Stevens et al. (1986) proposed three reasons for the lack of findings in their study. First, the MRI was insensitive with respect to the detection of lesions of the optic nerves. Second, they did not image the spinal cord; a site which is often associated with the physical symptoms of MS. Last, their clinical methods were insensitive at establishing neurological involvement (i.e. they relied on patient history or subjective interpretation rather than formal testing). Reese et al. (1986) listed the lack of detection by MRI of small lesions in the brainstem, cerebellum, and spinal cord, as a potential reason for the lack of correlations. Another reason for the lack of findings not cited by the above authors is also related to the underdeveloped MRI technology of that time period. Specifically, these studies used only non-contrast enhanced T1 or T2 imaging. As noted above, active lesions are often only detected when contrast agents such as gadolinium are used.

Later studies, utilizing machines with field strengths of 0.6T or better, also yielded nonsignificant results. Correlations between MRI variables and disease activity were again weak. Using more advanced technology (i.e., gadolinium enhanced imaging). Frank, Stone, Smith, Albert, Maloni, and McFarland (1994) found that number and area of new lesions correlated with increases of 0.5 points in EDSS scores in 12 MS patients (i.e., new lesions predicted a clinical worsening of symptoms). However, the statistical procedure for arriving at this conclusion was not clearly indicated, so caution in interpretation is warranted. Correlations were also weak in a study which examined the relationship between number of lesions on T2-weighted MRI scans and EDSS scores,

despite a large sample size ($n=281$) (Filippi, Paty, Kappos, Barkhof, Compston, Thompson, Zhao, Wiles, McDonald, & Miller, 1995). The authors proposed several reasons for the unremarkable findings. First, the patient sample was characterized by variability with respect to disease course, disease duration, level of disability at baseline, and treatment. Second, inter-rater reliability was not assessed for MRI ratings. Third, medications which suppressed the immune system were used in some individuals, and the effects on disability and MRI activity have not been clearly established. Finally, the authors admit that the EDSS has limitations with respect to its ability to reliably measure clinical activity. Indeed, even experienced neurologists often differ in their ratings. In a third recent study, van Walderveen, Barkhof, Hommes, Polman, Tobi, Frequin, and Valk (1995) found significant, but weak, correlations between total lesion area on T2-weighted images and EDSS score at baseline. However, no correlations were noted with respect to the change in these variables over time, such that changes in pathology did not predict changes in clinical status. The authors suggested that this may have been due to the fact that their patients' disease course remained relatively stable throughout the study period. Miller (1994) proposed five other reasons for the small or nonexistent correlations between MRI and clinical disability. First, inaccuracies may have occurred in the measurement of lesion load. Second, patients studied have differed widely with respect to disease duration. Third, longitudinal studies have been conducted over too short a time period. Fourth, disability is often related to spinal cord lesions which are not accurately imaged. Finally, Miller (1994) suggested that lesions themselves can be quite heterogeneous and yet look similar on an MRI image.

The relationship between MRI variables and clinical status is clearly weak at best. As suggested by Filippi et al. (1995) the EDSS is not the ideal measure of disease activity. As will be noted in detail below, studies have demonstrated that neuropsychological assessment is a proven method for detecting the cognitive changes associated with MS. Thus, lesions that are considered as “clinically silent” due to lack of correlation with the (primarily) physical symptoms documented in a neurological exam, may in fact, be related to the more subtle cognitive functions that are assessed by a neuropsychologist. Frank et al. (1994) also noted that a neuropsychological assessment may provide useful information in this regard.

It was postulated that neuropsychological measures were likely to be more sensitive to cognitive deterioration in MS than a standard neurological exam. A recent study addressed this issue by comparing the sensitivity of the MMSE (an instrument often used as part of a standard neurological exam to assess cognitive function) to a neuropsychological test battery, with respect to their ability to detect cognitive impairment in MS. The results were striking. The mean MMSE score for the MS patients fell in the normal range despite significant impairment demonstrated on neuropsychological measures. The authors propose several reasons for the insensitivity of the MMSE. “The MMSE does not measure speed of information processing or abstract reasoning. Its scant assessment of memory may not be of sufficient difficulty or complexity to capture the deficits in rapid encoding and the delay in retrieval that are features of subcortical dementia. The MMSE addresses certain basic language skills, but does not adequately assess naming or verbal fluency, which appear to be disrupted by

white matter lesions” (Swirsky-Sacchetti, Field, Mitchell, Seward, Lublin, Knobler, & Gonzalez, 1992, p.785). When total lesion area on MRI was examined, a significant correlation was found with several neuropsychological variables (i.e., memory, speed of information processing, abstract reasoning, naming/verbal fluency, visual perceptual organization). No relationship was found between MMSE performance and total lesion area. Tsolaki, Drevelegas, Karachristianou, Kapinas, Divanoglou, and Routsonis (1994) also found no relationship between the MMSE and MRI findings. Thus, neuropsychology appears to be more promising with respect to potential for correlation with pathology.

CHAPTER 3

NEUROPSYCHOLOGICAL RESEARCH

Although the majority of the symptoms of MS presented above can be documented in a standard neurological exam, research in the last few decades has revealed that individuals with MS may present with subtle cognitive changes that are only uncovered through more thorough neuropsychological testing (Peyser, 1984). These deficits have far-reaching effects with respect to the individual's quality of life. Specifically, Rao, Leo, Ellington, Nauertz, Bernardin, and Unverzagt (1991) found that, when compared to cognitively intact MS patients, those with cognitive deficits "were less likely to be working, engaged in fewer social and avocational activities, reported more sexual dysfunction, experienced greater difficulty in performing routine household tasks, and exhibited more psychopathology" (p.692). Schanke, Grimsmo, and Reiersen (1993) also documented the relationship between cognitive impairment and failure on driving examinations, another variable which impacts significantly on quality of life. Given the extensive debilitating effects of cognitive impairment, a review of the specific deficits is warranted. What follows is a review of the most relevant neuropsychological literature. Although early studies simply confirmed that MS patients do indeed have "brain damage" (Bertrando, Maffei, Ghezzi, 1983), or focused on poor performance on motor and psychomotor tasks (Reitan, Reed, & Dyken, 1971; Beatty & Gange, 1977), later studies were able to address more specific cognitive issues so that a profile of neuropsychological impairment in MS has begun to be established.

Subcortical Dementia

Despite the connotations inherent in the name, the term *subcortical dementia* is intended to represent a *clinical*, rather than an anatomical, concept. This point was stressed repeatedly by Cummings and Benson (1984) in their review of the relevant literature, since several criticisms have been raised regarding this particular terminology. Although this pattern of cognitive dysfunction is observed in individuals who exhibit primarily subcortical organic compromise (i.e., striatum, thalamus, substantia nigra, subthalamic nucleus, ventral tegmental area, locus ceruleus, and deep hemispheric white matter tracts), the same symptoms may also be observed in individuals who have cortical involvement (Cummings & Benson, 1984). In particular, people with frontal lobe lesions may exhibit similar profiles. However, the frontal lobes are extensively connected to subcortical structures, and therefore, these structures are implicated by anatomical association. Cummings (1990) summarizes this by stating that the term “*subcortical dementia* does not imply that the pathological alterations associated with the clinical syndrome are necessarily confined to subcortical structures; on the other hand, subcortical dementia describes a clinical syndrome that *can* be produced by exclusively subcortical dysfunction and is unlike the symptom complexes produced by most disorders of the cerebral cortex” (p.4). The second terminological problem lies with the word *dementia*. Cummings (1990) acknowledged that the oftentimes subtle cognitive changes referred to under the guise of the term *dementia*, may not meet the diagnostic criteria for such, as outlined in the Diagnostic and Statistical Manual of Mental Disorders. However, individuals with such a diagnosis do meet the criteria of an “acquired persistent

disturbance in neuropsychological function involving at least three of the following spheres of mental activity: language, memory, visuospatial function, cognition (abstraction, judgement, mathematics, executive function), and personality or emotion” (Cummings, 1990, p.4). Thus, an individual may qualify for the classification of subcortical dementia, without the connotations of severely impaired functioning, as long as they exhibit deficits in at least three realms of cognition. Despite the obvious flaws associated with the terminology, subcortical dementia has become a universally recognized term representing a specific clinical constellation of symptoms.

The syndrome of subcortical dementia has been implicated in several disease clusters. Cummings (1990) noted that these symptoms can be observed in degenerative disorders (e.g., Parkinson`s disease, Huntington`s disease); vascular disorders (e.g., lacunar state, thalamic infarction); and metabolic disorders (e.g., Binswanger`s disease, hypoparathyroidism). Multiple Sclerosis has also been identified as a disease which may manifest itself in terms of a subcortical dementia syndrome. Indeed, although the literature has stressed the involvement of deep gray matter structures in this constellation of symptoms, demyelinating diseases have also been implicated (i.e., MS, AIDS encephalopathy). Rao (1986) was one of the first to identify MS as a potential member of this category.

Four symptoms that have been highlighted as characteristic of subcortical dementia are: 1. slowed processing, 2. forgetfulness, 3. impaired cognition (i.e., ability to manipulate acquired information), and 4. changes in personality (i.e., apathy, depression) (Cummings & Benson, 1984). Contrasts are often made between subcortical and cortical

dementias. The primary symptoms characteristic of cortical dementias such as Alzheimer's disease (i.e., aphasia, alexia, agnosia, amnesia), are not usually observed. In addition, the intellectual impairment is usually milder in subcortical dementia (Cummings & Benson, 1984). Cummings (1990) concisely contrasted the performance of these two groups of impaired individuals in table form (see Table 1).

A study which specifically addressed the differences between Alzheimer's disease (DAT) and MS, confirmed some of these differences. Filley, Heaton, Nelson, Burks, and Franklin (1989) directly compared the performance of these two clinical groups on a comprehensive battery of neuropsychological tests. Although the DAT group demonstrated a greater degree of impairment (i.e., dementia) overall, the MS group was more impaired with respect to sustained attention. The authors proposed an anatomical explanation (in keeping with the cortical-subcortical distinction) that might help explain their findings. They suggested that "there may be a disruption of diffuse attentional systems arising from the brain stem and terminating in the neocortex. Alternatively or in addition, there may be damage to pathways originating in prefrontal cortex and terminating in posterior cortical areas, systems also involved in attentional function" (Filley et al., 1989, p.160). Thus, the white matter plaques of MS "disconnect" the subcortical structures from the cortex. Despite this evidence in favour of the cortical-subcortical distinction, the authors suggest that the appropriate label for the syndromes may respectively be gray-matter dementia versus white-matter dementia.

Table 1.**Contrasting Characteristics of Cortical and Subcortical Dementia Syndromes**

Characteristic	Subcortical Dementia	Cortical Dementia
Language	No aphasia (anomia and comprehension deficit when dementia syndrome is severe)	Aphasia early
Memory	Recall impaired: recognition normal or better preserved than recall	Recall and recognition impaired
Visuospatial skills	Impaired	Impaired
Calculation	Preserved until late	Involved early
Frontal systems	Disproportionately affected compared with other neuropsychological abilities	Impaired to a degree consistent with involvement of other abilities
Speed of cognitive processing	Slowed early	Normal until late in disease course
Personality	Apathetic, inert	Unconcerned
Mood	Depressed	Euthymic
Speech	Dysarthric	Normal articulation until late
Posture	Bowed or extended	Upright
Coordination	Impaired	Normal until late
Adventitious movements	Present: chorea, tremor, tics, dystonia	Absent (myoclonus occurs in some cases of DAT)
Motor speed	Slowed	Normal

Cummings, 1990, p.7.

Although there are clearly differences in quality between cortical and subcortical dementia syndromes, differences have also been noted between diseases *within* the subcortical distinction. Caine, Bamford, Schiffer, Shoulson, and Levy (1986) compared the performance, on a neuropsychological test battery, of individuals with Huntington's disease (HD) and those with MS. Similar patterns of performance were noted; however, the HD group demonstrated greater impairment with respect to verbal and nonverbal memory, calculation, copying, and language usage. The authors suggested that the MS group was able to utilize normal strategies when performing tasks, but deficits in mental speed and retrieval difficulties, hindered their performance on cognitive tasks. The differences in performance (and severity) were likely the result of the unique pathological processes inherent in each disease. Specifically, the greater memory impairment in the HD group was linked to striatal dysfunction. Thus, although specific neuropsychological deficits can be expected for individuals with MS based on its classification as a subcortical dementia, we can expect that each disease process can produce its own unique constellation of symptoms related to that syndrome's particular anatomical profile.

Given that the neuropsychological symptoms inherent to MS can be interpreted within the context of subcortical dementia, the review of the relevant assessment literature will be structured in such a way as to demonstrate this. In other words, specific attention will be paid to: information processing speed, forgetfulness (i.e., impaired recall), impaired cognition, and changes in personality.

Attention and Information Processing Speed

The first characteristic symptom of subcortical dementia to be addressed in reference to MS, is a slowing down of the rate of information processing (bradyphrenia). Although this is a symptom that can have far-reaching implications with respect to performance on neuropsychological tests, it is observation of subjects' performance on tasks of attention that has allowed us greater insight into this particular deficit. Clinicians have documented MS patients as having attentional difficulties in both the auditory and visual domains (White & Kregel, 1995). Even patients with little white matter pathology may have difficulty with speeded attention tasks such as the Trail Making Test, Part B (White & Kregel, 1995). One of the first research studies to systematically study information processing speed in MS, used both the Sternberg Memory Scanning Paradigm (subjects must decide if a number on a computer screen was presented in an earlier set of numbers), and the Paced Auditory Serial Addition Test (PASAT) (subjects are required to perform rapid serial additions with varied presentation rates) (Litvan, Grafman, Vendrell, & Martinez, 1988). The MS patients (some with relapsing-remitting courses and some with chronic-progressive courses) were impaired on the PASAT, but performed within normal limits on the Sternberg paradigm. The authors proposed that the discrepant findings were a result of differential task complexity. The Sternberg paradigm requires only one cognitive process; namely, a mental scanning of digits held in short-term memory. However, the PASAT requires three identified cognitive processes: "lexical activation of a set of numbers that, due to interference of an intervening computation, exceeds the limits of the span of apprehension; procedural activation of a

number computation process (addition); and fact retrieval to produce the correct addition answer" (p.284). The authors interpreted the results as suggesting that their MS subjects suffered from a working memory deficit, "because of cognitive resource limitations (i.e., a reduction in the number of cognitive processes that could be simultaneously activated)" (p.284).

In contrast to the above study, Rao, St.Aubin-Faubert, & Leo (1989) reported impaired performance on the Sternberg paradigm in their group of population-based MS patients. As such, the mechanism proposed by Litvan et al., (1988), cited above, may not be a suitable explanation. Rao et al., (1989) suggest that "while the [primary memory] storage capacity and the rate of forgetting from [primary memory] are intact in patients with MS, the rate at which this information is accessed from [primary memory] is deficient" (p.475). Whereas Litvan et al., (1988) proposed that working memory capacity is, in a sense, "overloaded" in individuals with MS, Rao et al. (1989) viewed the problem as one of rate of access from memory.

Kujala, Portin, Revonsuo, & Ruutinen (1994) are satisfied with neither explanation, and suggest that there are methodological difficulties with the above studies. and thus, the problem is confounded. The authors suggest that information processing can be broken down into three different stages, or aspects. First, *automatic processing*; an unconscious process that does not impinge upon working memory (e.g., recognition of numbers). Second, *controlled processing*; a conscious process that does rely upon both attention and working memory (e.g., subjects respond to a question such as, "is 2 greater than 9"). Third, is simple *motor programming* (e.g., the time it takes to plan and activate

a motor response). The authors divided their MS patients into two groups: those with mild cognitive deterioration, and those with preserved cognitive functioning. With the help of specially-designed computer paradigms which allowed the authors to partial out the effects of each of the above processes, results revealed that cognitively deteriorated MS subjects perform more poorly than controls in all three aspects of information processing, whereas the MS subjects with preserved functioning performed below controls on only the automatic processing component. The authors proposed that the difference between the two groups of MS patients may be reflective of more white matter pathology in the cognitively deteriorated group. Although this seems reasonable, further study, which could evaluate the relationship between white-matter pathology and degree of processing deficits, is warranted (i.e., a study which could correlate MRI-documented pathology with attentional measures).

In a follow-up study, Kujala, Portin, Revonsuo, & Ruutinen (1995) examined information processing in the same two groups of MS patients using standardized neuropsychological measures more commonly used in clinical settings (i.e., Paced Auditory Serial Addition Test [PASAT], Stroop Test). The MS patients with preserved functioning did not differ from controls; however, the cognitively deteriorated MS patients exhibited slowness on each of the two above-named measures. In contrast, on a test designed to assess a further component of *fatigue*, both patient groups performed below controls. Thus, when assessing MS patients on attentional measures, this potentially confounding variable must be taken into account.

Another study which used clinical measures of information processing speed, found similar results (Beatty, Goodkin, Monson, Beatty, Hertsgaard, 1988). Patients with chronic progressive MS performed below normal controls on the Symbol-Digit Modalities Test and verbal fluency measures. The former measure brings up another methodological complication, because performance on this task is potentially confounded by the motoric difficulties concomitant with MS. Based on their data, Beatty et al. (1988) postulated that greater than 75% of patients with chronic progressive MS can be expected to demonstrate diminished information processing speed. Other studies have also documented diminished verbal fluency scores (Klonoff, Clark, Oger, Paty, & Li, 1999; van den Burg, van Zomeren, Minderhoud, Prange, & Meijer, 1987); a task which demands rapid lexical access. Another task which demands rapid information processing speed is the Trail Making Test. Although this measure is confounded by motoric demands, poor performance has been documented even when motor performance is partialled out (Heaton, Nelson, Thompson, Burks, & Franklin, 1985).

Regardless of the contradictory explanations of the root cause of the problem, all of the above studies have provided support to the hypothesis that individuals with MS do present with a reduced capacity to rapidly process information. Thus, the supposition that individuals with MS will present with this aspect of the subcortical dementia profile, is supported in the literature.

Memory

Another hallmark characteristic of subcortical dementia is *forgetfulness*. This term implies that any difficulties with memory will occur at the level of recall rather than

encoding, thus differentiating the problem from amnesia where both aspects are impaired. Therefore, information can be learned and stored, but retrieval from storage is somehow deficient. A review of the literature which addresses memory and MS will help determine whether this pattern holds true from an empirical standpoint.

Although early studies of cognitive functioning in MS alluded to memory difficulties (i.e., poor recall from short-term memory) (Beatty & Gange, 1977), Grant, McDonald, Trimble, Smith, and Reed (1984) conducted one of the first studies to systematically assess this proposition. They tested MS patients in the early and middle phases of the disease on portions of the Wechsler Memory Scale (WMS) (using non-standardized procedures) and on a version of the Brown-Peterson paradigm. Results revealed that the MS patients performed more poorly than controls on each measure in both the verbal and visual modalities, suggesting poor immediate and delayed recall, poor learning, and a vulnerability to the effects of proactive interference. Other authors have also documented diminished performance on the Brown-Peterson paradigm (Beatty et al., 1988). Grant et al. (1984) found a significant positive correlation between short-term memory difficulties and number of years of active disease. Difficulties were also noted to be greater during more active phases of the disease. The authors urged future investigators to examine these latter findings more carefully using new imaging technology. For instance, the use of gadolinium enhanced MRI scans would allow a more direct measure of current disease activity.

A second study examining patterns of memory disturbance utilized a chronic-progressive sample of MS patients (Rao, Hammeke, McQuillen, Khatri, & Lloyd, 1984).

Deficiencies were found at the level of encoding and recall, but the findings also suggested “that, while the rate of acquisition of verbal material is relatively preserved, patients with MS are more susceptible to the effects of proactive and retroactive interference” (p.628). Thus, the encoding difficulties may reflect a greater vulnerability to distraction in the initial stages of learning (i.e., if no distraction is present, then encoding may be intact). Further analyses of these data revealed three distinct clusters of MS patients; each with differing profiles. The first group demonstrated moderate to severe problems with immediate and delayed memory, in addition to an atypical personality pattern (a “conversion” profile). Patients in cluster 2 demonstrated mild memory disturbances which may have been related to psychoactive medication use. These patients were also depressed. Finally, the third cluster consisted of patients who demonstrated normal memory functioning and a healthy personality profile. Once again, imaging studies would prove helpful here in examining potential pathological substrates for these distinct clusters.

An independent study by Fischer (1988) also documented three clusters of MS patients with varying memory performance, similar to those found by Rao et al. (1984). Using scores derived from the Wechsler Memory Scale - Revised (WMS-R), Fischer documented one cluster of patients (20% of 45 MS patients) who demonstrated global deficits (i.e., attention/short-term memory and learning), with slightly greater emphasis on visual impairments. A second group (56%) exhibited a milder impairment of learning. Attention and short-term memory were intact. These difficulties were not correlated with psychoactive medication use (as postulated above). The last cluster of patients (24%),

were intact on all measures when compared to controls. The degree of memory impairment was not correlated with disease duration, degree of disability, medication status, or depression. A second independent study also found three similar patterns of memory performance in MS patients. Minden, Moes, Orav, Kaplan, and Reich (1990) noted that 30% of their sample of 50 MS patients were severely impaired (i.e., greater than 2 standard deviations below normal controls), 30% were moderately impaired (i.e., between 1 and 2 standard deviations below controls), and 40% with minimal or no impairment (i.e., less than 1 standard deviation from controls). Future studies which could examine the underlying pathological profiles of each cluster are again warranted.

Fischer (1988) also described additional findings from her study. First, she noted that the MS patients performed significantly more poorly overall on the WMS-R, than normal controls. However, when the actual mean scores are examined, it is clear that the MS group performed within normal limits from a clinical standpoint. Thus, although their scores are statistically diminished relative to controls, one cannot conclude that memory is "impaired" in the MS patients. Rather, it would perhaps be more appropriate to state that memory is "diminished". That being understood, Fischer (1988) goes on to report that the MS group also performed more poorly than controls with respect to the learning of new information and delayed recall. These findings were consistent with both verbal and nonverbal material. The one exception to this rule is in the area of attention. Specifically, MS patients demonstrated diminished performance on digit span tasks, but not on the comparable visual span tasks. She proposed that the reason for the lack of impairment in the visual realm, may be the result of greater interference from the

environment on the digit task. In other words, when presented with a series of numbers, subjects may be distracted by phone numbers or significant dates, whereas the visual span task is more novel. Fischer (1988) concedes that other studies did not find a reduced digit span, but she stresses that this may be an artifact of the manner in which the data was analysed. She recommended that Digits Forward be analysed separately from Digits Backward.

Further insight with respect to encoding of information was provided by Carroll, Gates, and Roldan (1984). They presented MS patients with both word and picture recognition tasks. Results revealed that patients could encode information relatively well (i.e. they were able to respond in the affirmative to pictures they saw), but their performance was impeded when semantically-related distractors were introduced. In other words, they responded in a false positive manner to items that were not presented in the learning trial, but were from the same semantic category as the learned items. This provides further support to the notion that MS patients can learn adequately in conditions in which distraction is at a minimum, but performance declines with interference. Another way to conceptualize this problem is that MS patients are unable to properly filter out irrelevant material. However, other studies have demonstrated poor learning in MS patients compared to controls despite the absence of distraction (Heaton et al., 1985; van den Burg et al., 1987; Klonoff et al., 1991).

Encoding difficulties were not found in a study examining the performance of 50 MS patients compared to normal controls on a variety of neuropsychological measures (Minden et al., 1990). Although MS patients demonstrated poorer recall than controls,

they were able to learn information at a comparable rate. Additionally, the MS patients were no more affected by proactive or retroactive interference than controls (a finding which runs contrary to those discussed above). Cueing and forced choice procedures allowed patients to improve their performance on all but the most difficult tasks. Additionally, memory was noted to be correlated with lower socioeconomic status, a chronic-progressive disease course, and use of anti-anxiety medication.

Litvan et al., (1988) approached memory and MS from a theoretical perspective. They decided to examine working memory, which they defined as “a set of limited-capacity subsystems that constitute a “central executive” attentional-gating system that controls slave systems that specialize in different types of temporary storage, including a speech-based “articulatory loop” associated with subvocal rehearsal and a visuospatial “scratch pad” that temporarily stores visual information in an activated state (perhaps like an imagined icon)” (Litvan et al., 1988, p.607). According to results on tasks derived from the Brown-Peterson paradigm, and Baddeley’s working memory tasks, as well as standardized neuropsychological measures, the authors documented memory problems in three different areas. First, problems were noted with respect to processing information at the level of the articulatory-loop noted above. Second, MS patients also had difficulty retrieving information from long-term store. Last, they were impaired with respect to their ability to rapidly process verbal information. The authors propose that their findings are more consistent with poor encoding, rather than poor recall (since the forgetting rate of the MS patients was consistent with controls). They argue that this interpretation has a neuroanatomical basis. Since MS pathology is in white matter (responsible for

transmission of information) rather than gray matter (presumably where knowledge representations are stored), MS patients are:

“expected to demonstrate cognitive deficits in components of an information processing system that are responsible for transmitting information for activation or rehearsal purposes. Thus, it is predictable that patients with MS would be more impaired on tasks that require temporary storage of information during encoding rather than recall or recognition of information held in long-term memory” (Litvan et al., 1988, p.610).

The same theoretical assumptions were also held by D’Esposito, Onishi, Thompson, Robinson, Armstrong, and Grossman (1996). The performance of their MS patients declined significantly on a cognitive task, relative to controls, when a second task was introduced. The authors proposed that the addition of the second task placed increased demands on the central executive which is “responsible for allocating appropriate attentional resources in working memory during cognitive challenges” (D’Esposito et al., 1996, p.54). Thus, these two studies provide support to the notion that working memory deficits are also characteristic of individuals with MS.

A review of the memory literature thus leaves us with mixed results. Although there is certainly support for the “forgetfulness” of subcortical dementia postulated by Cummings and Benson (1984), some authors have also reported encoding difficulties, seemingly more consistent with a cortical dementia profile. White & Kregel (1995) propose that the encoding difficulties may, in fact, stem from *inefficient* encoding and slowed information processing, and that with repeated exposure proper encoding, or learning, of information is possible.

Cognition, Problem Solving, and Executive Functioning

In their discussion of subcortical dementia, Cummings and Benson (1984) stated that one of the hallmarks of this syndrome is impaired cognition. They defined the term *cognition* as “the ability to manipulate acquired knowledge” and the “ability to generate problem-solving strategies” (p.874). These can be considered as *executive* or conceptual functions. Two tests that have been used to assess these functions are the Halstead Category Test, and the Wisconsin Card Sorting Test (WCST). In his comprehensive review of the neuropsychological literature on MS, Rao (1986) noted that several studies documented impaired functioning of individuals with MS on the Category Test; however, he argued that that particular test is not as useful as the WCST, because it yields only one measure of performance (i.e. total errors). For instance, although Reitan et al., (1971) reported that MS patients scored below controls on the Category Test, their performance remained within normal limits. Klonoff et al., (1991) found no difference, on this measure, between controls and mildly impaired MS patients, whereas Heaton et al. (1985) did find that MS patients performed more poorly than controls. Thus, Rao, Hammeke, and Speech (1987) examined the performance of both relapsing-remitting and chronic-progressive MS patients on the, presumably, more sensitive WCST. Only chronic-progressive patients were found to exhibit deficits on this measure. Specifically, they exhibited a greater tendency towards perseverative responding than did control patients with chronic pain. Thus, the findings suggested that the impaired performance of individuals with MS on these tasks was a result of “an impaired ability to shift cognitive sets in response to negative feedback” (Rao et al., 1987, p.264). Impaired performance

on the WCST was also documented by Minden et al. (1990). Rao, Hammeke, Glatt, McQuillen, Khatri, Rhodes, and Pollard (1984) also reported similar conceptual difficulties using an independent measure, suggesting an inability of the chronic-progressive MS patients to benefit from verbal feedback, leading to an inability to shift mental sets. Other authors have also focused on the perseverative difficulties demonstrated on these tasks (White & Krenzel, 1995).

Although similar findings were documented by Beatty and Monson (1996), these authors argue for a different interpretation of the results. They compared the performance of chronic-progressive and relapsing-remitting MS patients on both the WCST and the California Card Sorting Test (CCST). The authors argue that "measures of perseveration and concept achievement on the WCST are not statistically independent, whereas on the CCST these measures are much less strongly related" (p.138). Although a lengthy description of the latter measure is beyond the scope of this discussion, a more detailed analysis of performance is possible with the CCST. MS patients demonstrated impaired problem solving on both measures. Specifically, they made more perseverative responses and errors and achieved fewer categories than controls on the WCST, but similar perseverative problems were *not* documented on the CCST. However, their performance was impaired because they attempted fewer sorts and achieved fewer correct sorts (indicative of conceptual difficulties). The authors argue that the perseverative problems noted on the WCST are not indicative of difficulties shifting set per se, but rather, are more suggestive of a difficulty in forming concepts. This interpretation was given further support in a second study assessing the performance of MS patients on the

Shipley Abstraction Test (in addition to the WCST and the CCST) (Beatty, Hames, Blanco, Paul, & Wilbanks, 1995). Results indicated that conceptual difficulties could account for the diminished performance of patients on all three measures. Interestingly, the authors suggested that there is a strong relationship between conceptual ability and information processing speed (both the CCST and the Shipley are timed), an interpretation that would provide further support to the subcortical dementia profile, given that information processing speed is also a hallmark symptom. They also noted that the verbal abstraction deficits could not be accounted for by vocabulary deficits alone.

Depression

Affective symptoms have long been recognized as part of the MS profile. Feinstein (1995) reported that four possible alterations in affect have been associated with MS: euphoria, mania, pathological laughing and crying, and depression. For several years, euphoria was considered to be more prevalent in the MS population than depression. Indeed, euphoria was thought to be the principle psychiatric component. McNamara (1991) noted that the reduced focus on this symptom now is due to the fact that definitions of both euphoria and MS have evolved over time. For instance, what may have once been termed euphoria may now be called frontal lobe disinhibition, emotional incontinence, or pseudobulbar palsy; conditions with neurological, rather than psychiatric, substrates (McNamara, 1991). Additionally, distinctions may not have been made between euphoria and mania (associated with a bipolar disorder) (Minden & Schiffer, 1990). Conditions that may have once been diagnosed as MS, may have in fact, been

other neurological disorders. Regardless of the reasons why, attention in the recent past has shifted to the concept of depression as a cardinal symptom of MS. Estimates of the prevalence of depression in the MS population range from 27% to 54% (Minden & Schiffer, 1990). Stenager, Knudsen, and Jensen (1990) suggest "that about one quarter of MS patients will require admission to a psychiatric department at some point in their illness and that about two thirds will be found to have a psychiatric disorder, to a varying degree" (p.254).

Early work in this area led researchers to believe that depression was prominent in individuals with MS because they were reacting to a debilitating illness and the resulting life changes. However, over time, researchers have begun to realize that the picture is not so simple. One of the first "modern-day" studies to examine the link between MS and depression compared MS patients with patients suffering from other chronic neurological disease (Whitlock & Siskind, 1980). Subjects were interviewed regarding their experience of depression both before the onset of the illness, and subsequently. In addition, the Beck Depression Inventory was administered at the time of the interview. Results revealed that the MS patients had experienced more depressive episodes both before and after the onset of the illness, and they were also more depressed than controls at the time of the interview. This study demonstrated that depression could no longer solely be considered as a reaction to a debilitating illness, since comparably disabled controls did not show this pattern of affective disturbance. Future studies, with more sophisticated methodology, yielded similar results (Dalos, Rabins, Brooks, & O'Donnell, 1983; Minden & Schiffer, 1990; Schiffer, 1987). Indeed, one of the first studies to use

systematic psychiatric interviews, in addition to psychometric measures, to evaluate affective symptoms found higher prevalence rates of both depression and bipolar disorder in MS patients when compared to the general population (Joffe, Lippert, Gray, Sawa, & Horvath, 1987).

The first study to examine the link between depression and MS *prospectively* followed MS patients and spinal-cord injured controls every month for a year (Dalos et al., 1983). Subjects completed the 28-item subscale General Health Questionnaire (GHQ). Results again revealed that MS patients were more emotionally disturbed than controls. However, the findings also documented that emotional problems were more often associated with clinical exacerbations of MS than periods of remission. Although disease course clearly can impact the experience of depression in MS, the mechanism is unclear. The authors admitted that they were unable to determine “whether the degree of disturbance is correlated with the type or magnitude of new disability or with the location of new plaques” (Dalos et al., 1983, p.576). New MRI techniques using gadolinium enhancement would now allow a more direct measure of disease activity.

After a review of the relevant literature Garland and Zis (1991) proposed three hypothetical explanations for the relationship between depression and MS. First, the depression may be a reaction to the debilitating nature of the disease. Some individuals may be more psychologically and/or biologically predisposed than others, thereby accounting for the fact that not all MS patients develop depression. Second, depression may be a direct result of brain pathology. Lesions in relevant areas of the brain may produce affective symptoms. Third, there may be a genetic link between susceptibility to

MS and susceptibility to affective disorders. The picture is complicated further by the fact that some pharmaceutical treatments for MS (e.g., corticosteroids, baclofen) have been implicated as potential causes of depression (Garland & Zis, 1991; Whitlock & Siskind, 1980). Schiffer (1987) reminds readers that not all cases of depression can be classified in the same way. Although the results of studies which demonstrate a greater prevalence of depression in MS patients when compared to similarly disabled controls may point towards a neurological substrate for depression, this does not rule out the fact that a person may also (or alternatively) develop reactive symptoms of depression. After an extensive review of the relevant literature, Ron (1986) came to a similar conclusion regarding the etiology of depression. However, she pointed out that future studies utilizing technologically-advanced imaging techniques may allow us to more easily examine the relative contributions of organic pathology versus psychopathology. A review of the literature examining correlations between imaging and neuropsychological variables is discussed in detail below.

Logically, one would expect depression to impact negatively on neuropsychological test scores. Indeed, this has been documented by Beatty et al. (1988). They reported that depression and antidepressant use was correlated with test performance, so that neuropsychological impairments were more severe in patients with this profile. However, in a later study, Beatty, Goodkin, Hertsgaard, and Monson (1990) did not find this association. Despite these contradictory findings, it would be wise to consider the potential impact of depression in future studies in order to avoid potential confounds.

Although the picture of depression in MS is muddled by the various etiological arguments, these data confirm that this particular affective symptom is a significant part of the profile of this disease. The exhibition of depressive symptomatology is consistent with the subcortical dementia profile.

Other Neuropsychological Functions

Visual-spatial deficits have also been documented in individuals with MS. White and Krenzel (1996) suggest that these difficulties stem from the particular distribution of white matter lesions in some patients, (i.e., optic nerves and cerebellum). These deficits may lead to specific types of errors: "rotation of block designs or pieces of puzzles, "pull" to the red aspects of the Block Design stimuli, and poor visual-spatial planning or impaired sequencing" (White and Krenzel, 1995). These visual-spatial deficits may also contribute to difficulties with memory for visual material.

Although the findings of MS patients reviewed here are roughly consistent with that expected of a subcortical dementia profile, authors have also documented findings which could be considered inconsistent with this conclusion. For instance, although the chronic progressive patients tested by Beatty et al. (1988) did demonstrate a number of findings consistent with subcortical dementia (i.e., impaired attention, diminished recall, depression), they also exhibited deficits more consistent with a cortical dementia profile. Indeed, the more impaired patient group performed poorly on the Boston Naming Test, reflecting significant anomic difficulties.

Other authors suggest that verbal skills remain relatively intact in individuals with MS. Any difficulties observed may be the result of impaired attention and slowed mental

processing, rather than verbal deficits per se (White & Kregel, 1995). Difficulty on verbal tasks may also stem from motoric problems such as dysarthria and diminished graphomotor control (White & Kregel, 1995).

Results vary with respect to the impact of disease course on neuropsychological functioning. Where Beatty, et al. (1990) found no correlation between disease course (i.e. CP versus RR) and various neuropsychological variables, other authors found significant correlations (Heaton et al., 1985). Specifically, patients with CP MS performed worse than both RR MS patients and normal controls on the Category Test, Trailmaking, and language-based tasks (i.e. aphasia). Although both CP and RR MS patients were impaired overall compared with normal controls, the CP group demonstrated more severe cognitive deterioration. Further, Klonoff et al. (1991) documented that cognitive declines can take place even very early in the course of MS.

Conclusions Regarding MS and Subcortical Dementia

The literature on neuropsychological functioning in MS is varied. Although evidence for the forgetfulness associated with subcortical dementia has been clearly documented, additional memory difficulties at the level of encoding were also found. These latter deficits are more in keeping with a cortical dementia profile. In addition, some researchers have documented language impairments, also more in keeping with a cortical profile. It is likely that these discrepancies relate to the specific anatomical location of MS pathology. Some authors suggest that the pattern of deficits in individuals with MS is similar to that observed in individuals with Nonverbal Learning Disabilities, given their difficulties with “perceptual, motor, visual-spatial, executive, reasoning, and

affective functions” (White & Kregel, 1995, p.422). It is unrealistic to assume that all diseases and disorders presumed to represent forms of subcortical dementia will fit into the exact same clinical mold. Feinstein (1995) pointed out that although MS is similar in its behavioural expression of subcortical symptoms to Parkinson’s and Huntington’s diseases, it differs from those because it is primarily a white matter disease. Certainly, some room for individual variation among disease types must be recognized. Thus, the subcortical profile may serve as a base model for a typical MS profile, given that allowances can be made for individual differences (both between MS and other “subcortical” diseases, and between various types of MS itself).

Methodological Issues in Neuropsychological Research

There are a number of issues related to the methodology used in studies of MS patients that make it difficult to draw firm conclusions from neuropsychological studies. Rao (1986) places these issues into seven categories, all of which will be discussed here. The first category of difficulties relates to diagnostic issues. One problem with the diagnosis of MS is the fact that early diagnosis is very difficult. Often the cognitive changes are overlooked, or taken to be indicative of other pathological changes (i.e., stroke) (Rao, 1986). This suggests that studies assessing cognitive functioning in MS patients may be overlooking a large proportion of the population. Although in the past, these more subtle cognitive changes were overlooked, recent advances in diagnostic techniques (specifically MRI and CSF analysis) may reduce the number of individuals who are missed.

The second methodological issue addressed symptom variability. Studies have

demonstrated that MS patients exhibit a great deal of variability in cognitive skills (Rao, 1986). In fact, the cognitive abilities may not even conform to a normal distribution. Rao (1986) suggests three implications which result from symptom variability. The first is that large sample sizes must be utilized in order to expect to yield any group differences between MS patients and normals. Second, group mean comparisons are inadequate because they are likely to overlook the variability within each of the samples. Finally, studies should utilize within-patient, repeated measure designs when possible to reduce variability. Related to this point is the significant degree of heterogeneity within subject samples. Often researchers do not distinguish between patients with respect to disease course (i.e., RR versus CP). Thus, perhaps variation between disease types could be overlooked.

Sampling is a third methodological issue (Rao, 1986). Most neuropsychological studies rely on patient populations to obtain their sample. This recruitment procedure is inadequate because it ignores all individuals with MS who are not in active treatment. This may perhaps further a bias that the MS population is more impaired on average than they are in actual fact. Peyser, Rao, La Rocca and Kaplan (1990) suggest that we need "large-scale, population-based studies to provide accurate prevalence rates for neuropsychological problems, and to examine these rates in the context of disease and demographic factors" (p. 94).

A fourth difficulty relates to the effects of medication (Rao, 1986). Rao and his group found that some medication used to treat MS may have some effect on memory functioning. Given the fact that most individuals with MS are treated pharmacologically,

medication may always be a complicating factor. However, more studies are required which specifically address the effects of medication on neuropsychological functioning. If medication is unavoidable, researchers should include a breakdown of the medications used by each subject.

Affective difficulties often plague individuals with MS, which leads to the fifth methodological consideration. Rao (1986) suggests that this situation could have implications for neuropsychological findings. MS patients experiencing depression may exhibit more cognitive deficits than those who are not depressed, whether the effects be short- or long-term.

A sixth important point raised by Rao (1986) addresses the use of control groups. Many different types of controls are used by researchers studying MS, ranging from normals to individuals with other neurological impairments. Researchers must realize that there are potential difficulties with all types of controls, and the one most appropriate for a particular investigation should be that which most successfully allows for the hypothesis to be tested. For example, "Patients with psychiatric disturbances are effective in controlling for the effects of affective disturbance and medication usages [whereas normal controls do not], but do not control for unique sources of variance associated with their specific psychiatric condition, the effects of psychiatric hospitalization and institutionalization, and the effects of physical disability" (Rao, 1986, p.533). Rao's studies have utilized a control group consisting of chronic pain patients (Rao, Hammeke, Glatt, McQuillen, Khatri, Rhodes and Pollard, 1984). The rationale for the use of such a group is as follows:

"patient control subjects provide a more stringent test of group differences by controlling for numerous nonspecific illness-related factors that may potentially affect cognitive test performance (e.g. hospital inpatient status, stress associated with having a chronic physical illness, and use of prescribed psychoactive medications). Thus one may argue with a greater degree of confidence that the observed group differences in cognitive test performance are more likely the result of brain dysfunction" (Rao et al., 1987, p. 265).

Thus this group has a make-up such that it controls for several potential confounding variables.

The last methodological issue addressed by Rao (1986) is a result of the sensorimotor difficulties that MS patients experience. The measures that are chosen to evaluate the cognitive functioning of these individuals must therefore be as free from motoric demands as possible. Rao (1986) stresses that "it is clear that MS patients may perform poorly on these measures, but not exhibit evidence of cognitive dysfunction on other 'purer' tests of cognition" (p. 534).

Peyser et al., (1990) also address issues related to the methodology of research studies of MS. They stress the importance of using appropriately sensitive measures to assess cognitive functioning. For example, a neurologist may assess the patient using a mental status exam and state that cognitive processes are intact. The neuropsychologist is able to provide more insight into the details of cognitive functioning. Neuropsychological batteries are designed to pick up the subtle cognitive changes that a mental status exam cannot.

One final methodological concern is that there is very little uniformity between laboratories on how MS patients are tested (Peyser et al., 1990). Peyser et al. (1990)

suggest a battery of tests that they feel should be used by all researchers assessing the cognitive functioning of MS patients. If all researchers were to use these criteria, this would allow for a greater degree of comparison of findings across centres and studies (Peyser et al., 1990). The authors do not suggest that research should be limited to this battery, but rather it should be seen as a common starting point.

Factors Affecting Neuropsychological Profile

There are a number of factors that influence how an individual with MS performs on a neuropsychological test or battery. One of the most important determinants of neuropsychological functioning appears to be the course that the disease exhibits. Rao et al., (1987) assessed the neuropsychological functioning in one area of individuals with either relapsing-remitting (RRMS) or chronic-progressive MS (CPMS). They tested conceptual reasoning with the Wisconsin Card Sorting Test (WCST). In order to be successful on this measure the subject must demonstrate an ability to evaluate verbal feedback as well as mental flexibility. Both groups of MS patients were compared to a control group of subjects with chronic pain. Although the CPMS group did not make significantly more errors than the RRMS group, they did exhibit significantly more perseverative errors, suggesting a diminished ability to shift cognitive sets in response to the negative feedback provided by the examiner. The authors were concerned that variables such as length of illness and degree of physical disability might have an influence on performance. Results indicated that only clinical course affected outcome, with the CPMS group demonstrating a deficit in conceptual reasoning.

Discrepant findings were found by Beatty et al., (1990). They tested CPMS and

RRMS individuals on a variety of cognitive measures including the WCST. Disease course was not found to be correlated with performance even when perseverative errors were analyzed. The authors concluded that their "findings suggest that assigned disease type, even when operationally defined by objective criteria applied over a 2-year period, is of little value for clinicians who wish to estimate the current levels of cognitive functioning of their patients with MS (Beatty et al., 1990, p. 307). It is unclear why the two studies garnered different results. The authors suggest that perhaps the label of CP or RR was assigned too soon in the course of the illness, such that the two groups were not as distinct clinically as originally thought. If MS patients who had a longer duration of disability, and therefore a more reliable label, had been used in the study, perhaps the findings would have reflected those of Rao's group. Once again, MRI imaging may have proven useful here so that pathology in each group could be compared directly.

Biological factors are also found to affect performance on neuropsychological tests. Specifically, the degree of demyelination or the lesion load has been found to correlate with neuropsychological functioning. This will be discussed in detail below.

CHAPTER 4

NEURORADIOLOGICAL CORRELATES OF NEUROPSYCHOLOGICAL FUNCTIONING

Single Occasion Scanning

Early imaging studies which attempted to correlate pathology and neuropsychological variables relied primarily on findings from CT examinations. Some encouraging results were documented. Rao, Glatt, Hammeke, McQuillen, Khatri, Rhodes, and Pollard (1985) found that cognitive functions, such as memory and executive abilities, were associated with brain atrophy as measured by ventricular size. Another study found a relationship between brain involvement documented on CT and emotional distress (i.e., generalized anxiety) (Rabins, Brooks, O'Donnell, Pearlson, Moberg, Jubelt, Coyle, Dalos, & Folstein, 1986). Both of these studies were promising with respect to the notion that people with MS may demonstrate a subcortical dementia profile. The current section will focus on the relationship between pathological variables (as documented by MRI) and performance on neuropsychological tests. Although only minimal correlations were observed between MRI variables and disability ratings (see above), the following is an attempt to demonstrate the more significant findings in the neuropsychological literature.

Using both T1- and T2-weighted images, correlations were documented between degree of atrophy of the corpus callosum and the presence of dementia in MS (Huber, Paulson, Shuttleworth, Chakeres, Clapp, Pakalnis, Weiss, & Rammohan, 1987). Patients were considered to be "demented" according to the criteria of Cummings & Benson

(1984). Patients performed worse than controls in each of the following areas: orientation, calculation, recall, verbal fluency, auditory attention span, paired associate learning, and visuospatial abilities. The authors also noted greater depression in patients relative to controls. Certainly these findings are consistent with the subcortical dementia profile in that depression, diminished recall, and slow processing were noted; however, the study presents several shortcomings with respect to methodology. First, although the authors used standardized tests to assess neuropsychological functioning, these tests were administered in a non-standardized fashion (i.e., selected items administered rather than whole test). Second, the sample of MS patients was rather heterogeneous. No attempt was made to distinguish between disease course (i.e., RR versus CP), and degree of disability ranged from 1 to 9 on the EDSS (an extremely broad range). Finally, given that two different raters read the MRI scans, no measure of inter-rater reliability was utilized (i.e., the two ratings were averaged).

A second study, in which the authors professed to find evidence for a subcortical dementia profile, found a relationship between the number of abnormalities detected on MRI and the degree of cognitive impairment on neuropsychological tests (Medaer, Nelissen, Appel, Swerts, Geutjens, & Callaert, 1987). However, several methodological problems can be found. First, the authors stated that their findings supported a subcortical profile, but their test battery was incomplete. They did not assess executive abilities or emotional functioning; two areas that are characteristic of this profile. Second, the test battery was not consistent between patients (i.e., some were administered WAIS-R Performance items and some were not). Third, the MS patients

were separated into three groups based on cognitive functioning, but the criteria for this distinction was never made clear. Fourth, the authors did not clearly delineate which specific MRI variables contributed to the correlations found. Fifth, the patient sample was heterogeneous. Once again, disease course was not controlled for, and the duration of symptoms varied significantly (i.e., range of 2-28 years). Finally, the field strength of the MRI machine was lower than that recommended above (i.e., 0.15T, as opposed to 0.5T).

Franklin, Heaton, Nelson, Filley, and Seibert (1988) reported similar findings, but their study was more methodologically-sound. All chronic-progressive MS patients were administered a screening battery of neuropsychological tests developed specifically “to provide a brief, standardized assessment of a relatively broad range of abilities that can be affected by cerebral disorders: psychomotor speed, sequencing efficiency, visual attention, verbal learning and delayed recall, nonverbal learning and delayed recall, visuoconstructional skills, expressive and receptive language functions, and reading comprehension” (p.1826). The authors noted that the neuropsychological screening battery (NSB) was more sensitive to cognitive dysfunction in MS than was the Mini-Mental Status Examination (MMSE). In addition, results of the NSB were significantly correlated with cerebral lesions on MRI. The areas of greatest impairment in the MS patients were “psychomotor speed, sequencing efficiency, attention, efficiency of new learning, retention of recently learned information, and visuoconstructional skills” (p.1828). Consistent with the subcortical profile, language skills were intact. Some minor methodological problems with this study were as follows: the field strength of the

MRI was only 0.15T, and the authors did not report when in time the MRI was conducted in relation to when neuropsychological functions were assessed.

The above studies by Franklin et al. (1988) and Huber et al. (1987) have been further criticized on three other grounds (Rao, Leo, Haughton, St. Aubin-Faubert, & Bernardin, 1989). First, the MRI variables were not reflective of exact pathology, but rather, relied on rating scales. The element of human error is thus possible. Second, both studies used brief cognitive screening exams, so that some cognitive deficits may have been overlooked as a result. Third, neither study attempted to control for the effects of age and education; both variables that have been demonstrated to have an impact on neuropsychological test performance. Taking these three shortcomings into consideration, Rao et al. (1989) performed a methodologically elegant study (with the exception of a heterogeneous subject sample) examining the relationship between pathology documented by MRI and neuropsychological test performance. Using a multivariate stepwise multiple regression procedure which controlled for demographic variables, investigators found relationships between different MRI variables and various types of cognitive dysfunction. Specifically, Rao et al. (1989) found that total lesion area (TLA) predicted performance on measures of recent memory and abstract/conceptual reasoning, and that corpus callosum size (SCC) predicted information processing speed, sustained attention, rapid problem solving, and mental arithmetic. Both of these MRI variables also predicted performance on measures of verbal intelligence, linguistic processes, and visuospatial problem solving. The authors suggested that the fact that rapid problem solving tasks and sustained attention were correlated with callosal atrophy

suggests that these processes may rely upon “precisely timed interhemispheric communication that is disrupted by demyelinated callosal fiber tracts” (p.165). Once again, support was found for the supposition that individuals with MS may exhibit a subcortical dementia profile.

Similar findings were reported by Pelletier, Habib, Lyon-Caen, Salamon, Poncet, and Khalil (1993) and by Huber, Bornstein, Rammohan, Christy, Chakeres, and McGhee (1992). They too found that callosal atrophy was significantly correlated with cognitive impairment. However, the interpretation of the findings by Huber et al. (1992) differs from that of Rao’s group. Huber et al. (1992) reported a strong correlation between total lesion area and callosal atrophy. In their study, both of these MRI variables predicted the same pattern of global cognitive impairment. This brings into question Rao’s assumption that callosal atrophy selectively affects only rapid problem solving and attention, since other cognitive variables were equally as affected in the Huber et al. (1992) study.

Izquierdo, Campoy, Mir, Gonzalez, and Martinez-Parra (1991) found a relationship between a different pathological variable and cognitive dysfunction. Specifically, learning and memory impairments were secondary to periventricular lesion load. For data analysis, the authors used a stepwise regression process akin to that used by Rao et al. (1989), with one important distinction. Whereas Rao et al. (1989) used MRI variables as predictors of neuropsychological test performance, Izquierdo et al. (1991) used neuropsychological test performance as predictors of MRI variables. Nonetheless, both studies documented significant relationships between these two sets of variables. Another finding of this study, which is in contrast to earlier studies, is that MRI variables

correlated significantly with EDSS disability ratings. Despite these promising findings, this study continues to be plagued by methodological problems. First, the subject sample is heterogeneous with respect to disease course. Second, the method used to estimate IQ is questionable. Third, only one neuroradiologist rated the MRI scans. Finally, although controls were used, they were not matched to the patient sample on the basis of demographic variables.

A study which attempted to exert more control over their subject sample by using only patients with a relapsing-remitting course, and an EDSS score less than or equal to 6, yielded similar results (Anzola et al., 1990). They reported that patients who exhibited extensive periventricular demyelination performed poorly on neuropsychological measures of concept formation, non-verbal reasoning, and verbal recall. Thus, although a different MRI variable was utilized in this study, similar correlations with cognitive variables resulted. Although these findings are consistent with the subcortical profile, this study also yielded findings to the contrary, in that no correlation between MRI variables and depression were found. Tsolaki et al. (1994) also found no correlation between MRI findings and depression). A second study to use only patients with a relapsing-remitting course yielded similar results (Pozzilli et al., 1991), in that a relationship between periventricular involvement and cognitive impairment was documented. Patients performed worse than controls on measures of naming, verbal fluency, and verbal and visual memory. Contrary to the subcortical hypothesis, the authors proposed that the memory difficulties resulted from encoding difficulties. A third study examining only patients with a relapsing-remitting course found that the degree and

pattern of cognitive dysfunction varied as a function of pathological characteristics (Pugnetti et al., 1993). Specifically, a group of patients who presented with large discrete lesions demonstrated a mild loss of attentive and abstracting abilities, whereas both a group of patients with small discrete lesions and parenchymal atrophy and a group of patients with confluent lesions demonstrated poor attention, psychomotor retardation, slowed mentation, and visuospatial difficulties. This latter study demonstrated that patterns of decline in MS are varied, and appear to depend (at least in part) with the type of pathology present.

An ambitious project by Ryan, Clark, Klonoff, Li, and Paty (1996) provided further support to this last assertion that the pattern of cognitive impairment can vary significantly in MS. The authors suggested that the profile of cognitive impairment is dependent upon the idiosyncratic lesion patterns exhibited by each individual. With the aid of cluster analysis of the neuropsychological test results of 177 patients with relapsing-remitting MS, the authors found that two different patient groups exhibited moderate to severe declines in information processing efficiency, memory, and visual-spatial ability. Three other groups exhibited deficits in one or two of these same areas. Thus, rather than assuming that all individuals with MS present with the exact same subcortical dementia profile, it is more likely that individuals will exhibit only certain aspects of the profile that are consistent with their lesion distribution. In this study, lesions in the genu of the corpus callosum were associated with visuo-spatial impairment, and lesions in the left parietal area were associated with verbal learning. Although not specifically addressed by the authors, it is possible that patients are more heterogeneous

in the early stages of the disease when lesion distribution varies considerably, but as they acquire sufficient global damage, patients may eventually conform more completely to the subcortical profile.

Ron, Callanan, and Warrington (1991) attempted to improve on earlier studies with the inclusion of three separate control groups. In addition to being compared to both normal and physically disabled controls, MS patients were also compared to other patients with clinically isolated syndromes of the type seen in MS (e.g., optic neuritis). By the inclusion of this latter group, the authors hoped to gain some insight into the evolution of intellectual deterioration in MS. Results revealed that MS patients performed worse than controls in all psychometric functions assessed, with the exception of naming and verbal memory. Although the former finding is consistent with the subcortical profile, the lack of a verbal memory deficit was surprising. The most likely reason for this finding is that the authors used a recognition memory test rather than a free recall test. Since recognition tasks are easier, more subtle cognitive deterioration will not be identified. This study also examined the effects of psychiatric impairment on cognitive functioning. The authors found that the severity of psychiatric symptomatology was correlated with poorer overall cognitive performance. Higher MRI lesion scores also correlated significantly with poorer overall cognitive performance. Lastly, the performance of the clinically isolated syndrome group was intermediate between controls and MS patients. Results suggested that “with advancing disease, early attention deficits, which can be detected even in those with minimal neurological impairment, extend to involve memory and abstracting abilities” (Ron et al., 1991, p.66).

Serial Scanning

The first study to attempt to correlate serial MRI's with neuropsychological test performance was conducted by Mariani et al., (1991). They tested 19 MS patients with a relapsing-remitting course on two occasions, approximately 2 years apart. Unfortunately, the study yielded nonsignificant results. No significant correlations were found between change in MRI variables and change in neuropsychological variables. The lack of findings may relate in part to the methodological problems in the study. For instance, the first MRI and the first neuropsychological assessment occurred anywhere between 2 days and 6 months of each other. Given that MRI's can change within days, it is not surprising that adequate correlations between these findings were lacking. A second problem was that the time until the follow-up examinations was not consistent between subjects. Lastly, test order was not randomized, allowing for the possibility that fatigue confounded neuropsychological test performance. Despite these problems, the authors deserve credit as they were the first to attempt the examination over time, of the relationship between pathology and clinical symptomatology.

A second serial study also yielded nonsignificant results (Mattioli, Cappa, Cominelli, Capra, Marcianoc, & Gasparotti, 1993). Mattioli et al. (1993) assessed 9 individuals with relapsing-remitting MS on tests of verbal memory, non-verbal reasoning, visuo-spatial matching, concept formation, and affect. All subjects received MRI evaluations within one week of the neuropsychological testing. This appears to be the first study to utilize gadolinium-enhanced scans, thereby enabling the monitoring of *active* lesions, or current disease activity. Despite the improvements over the Mariani et

al. (1991) study, no significant correlation was found between the change in cognitive abilities and the change in pathology over time. Once again, there are several methodological shortcomings that may have contributed to the lack of significant results. First, the follow-up interval was only three months. This time period is considered to be insufficient according to the guidelines for clinical trials proposed by Miller et al. (1991). They recommend at least a 6 month follow-up interval. Second, the follow-up interval was inconsistent between subjects (i.e., ranging between 45 and 112 days). Third, test order was not randomized, thus fatigue may have artificially lowered scores on latter measures. Last, although the authors purported to measure acute lesion load, they did not include recurrent (but enhancing, therefore active) lesions in their calculation of current disease activity. They considered only those lesions which were not active on previous scans. Thus, some active disease activity was overlooked, perhaps contributing to the lack of correlations.

A third serial study was conducted by Feinstein, Kartsounis, Miller, Youl, and Ron (1992). Patients were not diagnosed with MS at the beginning of the study. Rather, they were diagnosed with clinically isolated lesions. But 54% of the subjects did progress to MS by the time of follow-up. The subjects were further subdivided into those with clinically isolated lesions, with relapsing-remitting MS, and with chronic-progressive MS.

Different slice thicknesses of noncontrast-enhanced MRI data at baseline and follow-up precluded the examination of the relationship between the change in pathology and the change in cognition over time. However, the authors did document some

cognitive deterioration over time. Specifically, there was an increase in psychiatric morbidity, and a deterioration in performance on tests of visual memory. The chronic-progressive group demonstrated a further deterioration with respect to auditory attention. With respect to correlations between pathology and cognitive disturbance, visual memory was found to correlate significantly with total MRI lesion score. Psychiatric status did not correlate with the lesion score. There was a nonsignificant trend for the T1 and T2 relaxation scores to be higher in MS patients when compared to normal controls. Methodological weaknesses in this study include: the lack of comparable MRI results at baseline and follow-up, the lack of contrast-enhancement, and the fact that some patients were prescribed anti-depressant medication during the study period. A significant improvement over past studies was the fact that MRI imaging and psychometric testing were conducted on the same day.

A second serial study by the same research group compared the MRI findings, and the performance on measures of attention and information processing speed, of 5 relapsing-remitting MS patients and 5 benign MS patients with that of matched controls, over a 6-month time period (Feinstein, Ron, & Thomson, 1993). The patient groups made more errors or performed more slowly when compared with controls; however, the small subject sample precluded the researchers from analysing their data statistically. Thus, the significance of these findings is unclear. The authors reported that those patients who demonstrated an increasing lesion load over time, exhibited a corresponding decrease, or a stability, in performance on some tasks of attention and information processing speed. In other words, they did not demonstrate the practice effects exhibited

by their pathologically-stable counterparts. Although this study improved on past research given that the MRI scans were obtained on the same day as psychometric testing, methodological limitations were evident. Specifically, there was a lack of statistical support for the authors' conclusions, and practice effects were evident given the frequency of the psychometric testing. These limitations, both acknowledged by the authors, reduce the generalizability of the findings.

CHAPTER 5

THE PRESENT INVESTIGATION

Rationale

Several investigators have demonstrated the link between multiple sclerosis and the subcortical dementia profile first espoused by Cummings and Benson (1984), but few have addressed this issue specifically. Indeed, although they may test one aspect of the profile, few researchers have tested MS patients with measures designed to assess each of the four affected areas in turn (i.e. information processing, memory, abstraction/cognition, and affect). Also, few investigators tested the stability of the profile across time.

The present study includes measures in each of these areas of functioning so that an adequate picture of neuropsychological functioning can be gleaned. In addition, subjects were tested on two occasions, six months apart. With respect to the subcortical profile, past studies have demonstrated that MS patients exhibit slowed processing (Beatty et al., 1988; Heaton et al., 1985; Kujala et al., 1994 & 1995; Litvan et al., 1988; Rao et al., 1989), forgetfulness and memory difficulties (D'Esposito et al., 1996; Fischer, 1988; Grant et al., 1984; Litvan et al., 1988; Minden et al., 1990; Rao et al., 1984), abstraction or executive functioning deficits (Beatty et al., 1995; Beatty & Monson, 1996; Heaton et al., 1985; Minden et al., 1990; Rao et al., 1984 & 1987), and affective difficulties (namely depression) (Dalos et al., 1983; Joffe et al., 1987; Minden & Schiffer, 1987; Schiffer, 1987; Whitlock & Siskind, 1980). Thus, in the current study, we can expect to find similar results. Specifically, it is proposed that the MS subjects tested will

exhibit at least one or more aspects of the subcortical dementia profile. Any changes in the profile observed over time, are expected to be associated with changes in the underlying pathology (see below).

The current study also corrects some of the methodological difficulties discussed by Rao (1986) in his review of prior MS research. Presently, patients are used as their own controls in a repeated measures design, affective difficulties are considered as part of the analysis, and where possible, measures are used which do not have a motor component (and thus, are not confounded by the physical limitations of these patients). Rao et al. (1987) demonstrated that significant differences in profile can be observed in MS patients with varying disease course. Indeed, chronic-progressive patients were demonstrated to be more significantly impaired than controls on some measures. Prior researchers have often failed to consider the distinction between relapsing-remitting and chronic-progressive groups (a potentially confounding variable), and have used a heterogeneous group of individuals which included patients with both disease courses. The present study assesses only relapsing-remitting patients in the early stages of their disease. Thus, although results are only generalizable to this population, the reliability of the results are likely greater with the addition of this control. This study also builds upon prior studies by the administration of a comprehensive battery of neuropsychological tests. Most studies have focused on one particular area of functioning (e.g., memory or executive functioning). The current project attempts to provide a broader picture of neuropsychological functioning.

Several investigators have proposed that MS pathology detected by MRI is a

better indicator of disease activity than clinical signs and symptoms because lesions can be present without corresponding physical symptomatology (Baum et al., 1990; Capra et al., 1992; Isaac et al., 1988; McDonald et al., 1994; Miller et al., 1994; Paty et al., 1994; Truyen et al., 1991; Willoughby et al., 1989). Previous studies that have examined this relationship between MRI variables and clinical disability have been fraught with methodological difficulties. The current study is an attempt to improve upon prior research in order to examine this potential relationship between MRI variables and clinical disability as measured by the EDSS. Several studies have been conducted that have yielded nonsignificant results (Filippi et al., 1995; Frank et al., 1994; Jacobs et al., 1986; Reese et al., 1986; Stevens et al., 1986; van Walderveen et al., 1995) because correlations have been weak or absent. Several reasons have been hypothesized as to why this has been so (see above, p.36). The current study has several advantages that may help to increase the magnitude of the relationship between MRI findings and clinical disability. Specifically, subjects were more homogeneous with respect to disease course and duration, and MRI technology has become more advanced. Therefore, it is expected that significant correlations will be found between active lesion load (ALL) on MRI and clinical disability.

As discussed earlier, there is good reason to expect that correlations will be greater between MRI variables and neuropsychological findings than between MRI variables and neurological disability ratings (Swirsky-Sacchetti et al., 1992). Indeed, a number of investigators have demonstrated a significant positive relationship between degree of pathology on MRI and neuropsychological findings (Anzola et al., 1990;

Franklin et al., 1988; Huber et al., 1987 & 1992; Izquierdo et al., 1991; Medaer et al., 1987; Pelletier et al., 1993; Pozzilli et al., 1991; Pugnetti et al., 1993; Rao et al., 1989; Ron et al., 1991; Ryan et al., 1996). The current study improves upon prior studies in several ways.

First, the contrast agent gadolinium was utilized, allowing for the calculation of a measure of ALL. Previous research has demonstrated that gadolinium enhanced T1-weighted imaging is better than non-contrast enhanced imaging at detecting new active lesions and reactivated older lesions (Drayer & Barrett, 1984; Francis et al., 1995; Miller, 1994; Miller et al., 1991; Rudick, 1992). However, most studies have relied on T2-weighted imaging technology and, thus, correlations may have been artificially low due to the fact that active lesions went undetected. The detection of current pathological activity will more likely provide a better correlation with current neuropsychological deficits than old (non-active) lesions (i.e., patients may have found ways to compensate for older lesions). In this case, ALL includes new lesions as well as recurrent and enlarging enhanced lesions. This approach is consistent with the recommendations of Miller et al. (1993), and is an improvement over Mattioli et al. (1993) because they did not consider recurrent (yet still active) lesions in their analysis.

Second, the current neuropsychological testing was conducted within 48 hours (72 hours in one case) of the MRI examination. Although research has shown that lesions can be active for only a short period of time (Francis et al., 1995; Thompson et al., 1992), the majority of correlative studies to date have often overlooked this fact and completed the different examinations several days, or even months apart.

Finally, the current study improves on previous research in that an attempt was made to meet the guidelines for clinical trials proposed by Miller et al. (1991). Specifically, this study meets guidelines with respect to the following: sufficient field strength of MRI equipment, the use of contrast enhancement, inclusion of subjects with a relapsing-remitting course, clinical assessments conducted in conjunction with serial scanning, sufficient study duration (i.e., 6 months), repeated measures design, and recording of all new, enlarging, and enhancing lesions. Thus, given these improvements over prior research, it was expected that active lesion load as documented on MRI, would correlate positively with the degree of neuropsychological impairment both at time 1 and time 2.

To date, there have been only three studies that examined the relationship between MRI and neuropsychological variables in MS patients over time (Feinstein et al., 1993; Mariani et al., 1991; Mattioli et al., 1993). None of the studies yielded significant results with respect to the change in pathology and the change in cognition over time. The current study improves upon previous studies in three ways: First, as in the Feinstein et al. (1993) study, the time interval between MRI and neuropsychological testing is shorter. In the Mariani et al. (1991) study, time between the two examinations ranged between 2 days and 6 months. Second, follow-up examinations were conducted 6 months from baseline for all subjects. Both Mariani et al. (1991) and Mattioli et al. (1993) were inconsistent between subjects with respect to follow-up times. Last, both Mariani et al. (1991) and Mattioli et al. (1993) presented the neuropsychological tests in the same order for each patient, thus, the results of the latter tests may have been confounded by fatigue.

The current study corrected this by presenting tests in a more random fashion, both between subjects, and within subjects on the two test occasions.

Thus, it was expected that this study would find a positive relationship between the change in total lesion load (TLL) and the change in neuropsychological variables. For this analysis T2-weighted lesion load was chosen over ALL because it is more likely to reflect change in total pathology (or burden of disease). Different lesions may be active at time 1 and time 2, but no change would be reflected if ALL were the measure of choice. TLL is more likely to reflect global change. Despite the improvements in this study, any correlations found between change in MRI variables and change in neuropsychological variables are expected to be weak. This is due to the fact that the disease is not likely to progress significantly over the course of only 6 months (van Walderveen et al., 1995). However, any significant results found here may provide future researchers with enough evidence to consider this question to be of sufficient merit to warrant inclusion of similar measures in studies where longer follow-up is possible.

Hypotheses

1. Subjects will demonstrate at least one or more aspects of the subcortical dementia profile, including: slowed information processing, forgetfulness, decreased cognition or executive functioning, and/or affective disturbance.
2. The ALL will be positively correlated with the degree of disability as documented on the EDSS, at both baseline and follow-up. ALL will be calculated by adding the number of newly enhancing lesions to the number of persistently enhancing lesions (i.e., all those lesions that enhance on T1 with the use of gadolinium).
3. Active lesion load will be positively correlated with deficits in information processing speed, recall, executive functioning, and/or affect at both baseline and 6-month follow-up.
4. The change in TLL (i.e., burden of disease, or total surface area of lesions in mm²) on T2-weighted images will be correlated with the change in subcortical neuropsychological variables over time (i.e., between baseline and the 6-month follow-up).

CHAPTER 6

METHODOLOGY

Sample

Twelve adults (2 males, 10 females) with relapsing-remitting multiple sclerosis were enrolled as subjects. Subjects ranged in age from 21 to 48 years, with a mean age of 35.5 years. Education ranged from 12 to 18 years, with a mean level of 14 years. Five subjects had completed high school, 2 college, 4 university undergraduate programs, and one graduate program. Disease duration (from date of diagnosis) ranged from 0 (i.e., a few months prior to study onset) to 8 years, with a mean of 3 years. Symptom duration exceeded disease duration, and ranged from 0 (i.e., a few months prior to study onset) to 13 years. The symptom duration was subjectively rated by each patient. The mean amount of time between onset of symptoms and diagnosis was 2.08 years. Ten subjects were right-handed and two left-handed. Patients were recruited from the Multiple Sclerosis Clinic of the Ottawa General Hospital (a tertiary care facility). All subjects were also participants in a larger, multi-centre research study. Of the 16 patients enrolled in the larger study at the Ottawa General Hospital site, 12 also agreed to participate in the present investigation. In order to be considered, the patients had to meet the following inclusion criteria delineated by the larger study:

- provide written informed consent prior to all eligibility screening procedures
- men or women 18-55 years of age
- relapsing-remitting MS with or without secondary progression meeting criteria for clinically or laboratory supported definite MS (see Appendix C)
- Expanded Disability Status Scale(EDSS) score less than or equal to 5.5 (see Appendix D)
- history of MS of less than or equal to 10 years for patients with EDSS less than

or equal to 3

- two or more clinical exacerbations within the last 2 years prior to screening
- able and willing to undergo study procedures and to attend for treatment and follow-up

Subjects who met any of the following exclusion criteria, also delineated by the larger study, were not enrolled into the present study:

- current medical, neurological or psychiatric condition which could interfere with the evaluation of the patient's disease at baseline or at anytime throughout the study or which could impact on the patient's ability to remain in the study for the full study duration
- currently present with clinically significant laboratory abnormalities, including:
 - serum creatinine greater than 133 $\mu\text{mol/L}$ (1.5 mg%)
 - ASAT or ALAT greater than or equal to 2 times the upper limit of normal range
 - total bilirubin greater than 34 $\mu\text{mol/L}$ (2 mg%)
 - hemoglobin 20% below the lower limit of normal range
- women who are not surgically sterile or post menopausal (2 years amenorrhea), or who do not meet both criteria shown below:
 - have a negative pregnancy test at screening, and
 - use a reliable means of contraception for the entire duration of the study (hormonal contraception, intrauterine device, reliable mechanical barrier).
- currently using or prior use of drugs which may have an effect on MS including interferons, cyclophosphamide, azathioprine, etc., but with the exception of steroids for the treatment of exacerbations of MS. *In this latter circumstance, steroid must not be administered within 28 days of the screening MRI.*
- less than 28 days between the onset of improvement of all signs and symptoms attributable to an MS exacerbation and the screening visit.
- an exacerbation between screening and baseline.
- diagnosis compatible with primary progressive MS (i.e.: without history of remissions).
- patients who are unable to undergo MRI scanning i.e., patients with severe claustrophobia, with aneurysm clips, pacemakers, or patients with excessive movements.

Given the unusual geographic distribution of MS, patients were asked where they were born, and whether they made any significant moves, both before and after age 15. All but one were born in Canada, with the exception being born in Eastern Europe (i.e.

Poland). All moves, both before and after age 15 were within Canada, with the exception of the individual from Poland who moved to Canada after the age of 15.

Subjects were questioned regarding occupational status. Four were no longer working, and were receiving disability benefits. Of the remaining 8, 6 were employed in white collar occupations and 1 in a blue collar position, while 1 was unemployed. Four subjects reported some change in their employment or their ability to perform their job since the onset of MS.

With respect to the experience of stress in their lives, 6 subjects reported an increase in the perceived amount of stress since the onset of MS. Stressors generally fell within the following categories: occupation, children, interpersonal relationships, health, or finances. Subjects were also asked whether or not they perceived individuals or organizations in their environment as supportive. Ten subjects reported some form of social support, whereas two reported subjectively feeling no support from any source. Means of social support were as follows: parents, children, friends, secular organizations (e.g., MS Society), and health care providers. None reported feeling supported by religious organizations.

Subjects were questioned regarding their subjective opinion of their general mood in the recent past. Three subjects reported depressed mood, and two others reported feelings of anxiety. At baseline, none had sought treatment.

As noted above, Reder and Antel (1983) classified symptom types according to the anatomic locus of the lesions responsible. Subjects were questioned regarding their initial presenting symptoms and their current symptoms. With respect to those symptoms

present initially 9 reported spinal cord symptoms, 1 cerebellar, 3 optic nerve, and none brainstem or cortical. The pattern of current symptoms demonstrated a different distribution, with 12 reporting symptoms of the spinal cord, 5 cerebellum, 1 brainstem, 5 optic nerves, and 8 cortical.

Procedure

This study was approved by the Research Ethics Board of the Ottawa General Hospital (see Appendix E).

All patients enrolled in the larger study were provided with an information sheet outlining the current project (see Appendix F) by the Ottawa General Hospital MS Clinic Research Coordinator. The MS research coordinator then asked the subject if he/she was willing to be contacted regarding the present study. If he/she agreed, a member of the Neuropsychology research team (L.Smith-Walker, L.Della Malva, A.Tellier, B.Collins) then contacted the patient and explained the details of the study. Of the 16 patients enrolled in the larger study, two refused to be contacted, two declined after hearing the time demands of the study, and 12 agreed to participate. All subjects provided written informed consent (see Appendix G). No remuneration was provided for participation.

Patients were assessed at baseline and at follow-up, 24 weeks later. The assessment included an MRI evaluation performed on a 1.5 tesla superconductive magnet (Siemens system). Each patient underwent the following MRI scans at both baseline and follow-up: 1) proton density/T2 weighted scan, 2) T1 weighted unenhanced scan, and 3) T1 weighted gadolinium-enhanced scan. All scans were performed on a Tuesday. Patients underwent clinical neurological exams on the Thursday of the same week.

conducted by a neurologist with the MS clinic. Expanded Disability Status Scale (EDSS) assessments were administered both at screening and at follow-up. Although the EDSS scores at screening were compared to MRI examinations conducted at baseline, the EDSS score would not have changed during this time period because patients were excluded from the study if any exacerbations occurred between screening and baseline. Each patient also underwent a neuropsychological test battery within 48 hours of the MRI (with the exception of one patient who received the follow-up neuropsychological evaluation within 72 hours of the MRI).

At baseline, patients were given the option of completing the neuropsychological evaluation in one session or two. Testing time was approximately 5 hours in total. At follow-up, all neuropsychological evaluations were conducted in one session, lasting approximately 3 hours. The order of test presentation was randomized both within and between subjects, with one exception. In order to ensure a standard delay interval for verbal and visual memory tasks, the same measures were used during the delay periods (i.e., Gordon Diagnostic System, Wechsler Memory Scale - Revised [WMS-R] Digit Span and Visual Span). All patients were also provided with psychosocial self-report measures to complete at home and mail back to the investigators within one week. When possible, alternate forms of the same test (California Verbal Learning Test, Rey Visual Design Learning Test), or alternative tests considered to measure similar functions (Category Test and Wisconsin Card Sorting Test) were administered at follow-up in order to avoid practice effects.

The neuropsychological assessments were conducted by a member of the neuropsychology research team (L.Smith-Walker, L.Della Malva, A.Tellier, B. Collins). Test results were scored and were analysed statistically using the Statistical Package for the Social Sciences (SPSS for Windows). All MRI scans were analysed by the University of British Columbia MRI Analysis Group. The neuroradiologists were blind to all details of the study. All scans for any given patient were reviewed by the same observer to promote consistency of observation and recording. At the end of the study, a selected number of scans were re-evaluated to assure consistency of the readings over the study period. In the event of insufficient consistency of results, all scans would have been reviewed and the latter results would have been retained. The investigators of the larger study selected the scans for which repeat readings were done.

Upon completion of the follow-up neuropsychological evaluation, patients were provided with written feedback regarding their test performance. All were encouraged to contact the Neuropsychology research team if they had any questions regarding their results. All were given the option of including the results in their clinical file at the MS Clinic of the Ottawa General Hospital if they so wished.

Instruments and Measures

Several standardized neuropsychological measures were utilized to assess the following areas of functioning: attention and speed of information processing, memory, executive functioning, emotional functioning (i.e., depression, hopelessness, anxiety), and general intellectual functioning. See Appendix H for these measures.

Clinical Interview: All subjects were interviewed in order to determine basic background information (i.e., education, employment), medical history, family medical history, social functioning, and specifics of their disease (i.e., initial symptoms, date of diagnosis).

Stroop Color and Word Test: This is a test of sustained attention in the face of distraction which requires the subject to first name color words presented in a vertical array (i.e., red, green, blue), then name colors (a series of "X"s printed in red, green, or blue ink), and then name colors while being distracted by the words (i.e., red, green, and blue words printed in the three colors of ink, where the word does not match the color of ink with which the word is printed). Normative data is provided by the author for adults ranging in age from 16 to 80 years (Golden, 1978). A modified version of this test was also employed, as similar modifications have been shown to provide better discrimination between normals and mildly impaired individuals (Bohnen, Jolles, & Twijnstra, 1992). This latter version is the same as above, but adds a fourth component. The subject is required to perform the distracter task as above; however, when they come to a word with a box around it they are required to read the word rather than name the color. Thus, this adds a component of mental shifting to the task. For the current study, normative data for both the standard and modified versions were obtained from Blodgett (1996).

Wechsler Memory Scale-Revised (WMS-R) Digit Span and Visual Span: The digit span (DS) task requires the subject to repeat strings of numbers dictated by the examiner: first forward, and then backwards. The visual span (VS) task requires subjects to tap the same sequence of squares (presented randomly on a card) as the examiner: first forward,

and then backwards. These tasks assess attention span in both the auditory and visual modalities respectively. The WMS-R manual provides norms for adults aged 16 to 74 years of age based on a large normative sample considered representative of the U.S. population (Wechsler, 1987).

Gordon Diagnostic System (GDS): This measure is a microprocessor-based, portable unit used to assess attention, reaction time, and distractibility. It is a tool often used to assess individuals suspected of having attention deficit disorders. The subject is instructed to press a button when they see a “one” followed by a “nine” flash on the screen. For the current study, two separate conditions were presented. The first was a vigilance condition which required the subject to press the button in the above circumstances. The second was a distractibility condition which required the subject to press the button as above while other numbers flashed on either side of the numbers of interest. For both conditions, normative data is provided for the following: total correct (i.e., hits), total commissions (i.e., false positives), and mean latency of response (i.e., reaction time). Normative data is available for children, adolescents, adults and geriatric populations (Gordon, McClure, & Aylward, 1996).

Trail Making Test (Form A & B): Form A requires subjects to connect with pencil, circled numbers from 1 to 25. Form B requires the same motoric action but the subject connects numbers and letters in alternating sequence. The test is designed to assess speeded visual search, attention, mental flexibility, and motor speed. Several investigators have provided extensive normative data. The test is considered to be part of the Halstead-Reitan battery (Reitan & Wolfson, 1985). Normative data was obtained

from Stuss, Stethem, and Pelchat (1988).

Consonant Trigrams (Brown-Peterson Paradigm): This measure was based on a widely-used technique to study attention or working memory in the face of distraction. In this version, the subject is given three consonants and a number. The subject is required to count backwards from the number by three's until the examiner signals him/her to recite the three letters. Varying delays of 3, 9, and 18 seconds were utilized. Normative data for 9 and 18 second delays is provided by Stuss, Stethem, & Poirier (1987) for adults aged 16 to 69 years.

California Verbal Learning Test (CVLT): This is a test of verbal learning, recall, and recognition. Subjects are required to learn a list of grocery items over the course of five exposures to the material. The presentation of a second list allows examiners to assess recall in the face of interference. Both free-recall and cued-recall are administered after brief and long delays. Finally, subjects are also given a test of recognition. Grocery items are in four semantic categories in order to assess whether the subject can develop a strategy for learning based on semantic grouping of information. Normative data is available for males and females aged 17 to 80 (Delis, Kramer, Kaplan, & Ober, 1987). An alternate form, developed by the test authors, was utilized at the follow-up examination.

Rey Visual Design Learning Test (RVDLT): This test is similar to the CVLT, but assesses similar functions in the visual modality. The test was designed to assess immediate memory span, learning, and recognition memory. The subject is presented with 15 designs (on cards) sequentially over five trials. On each trial they are instructed

to draw as many of the designs as they can remember. Recall is assessed after short and long delays. Recognition is also assessed after a short and long delay. Normative data is available for adults aged 20 to 70+ years (Spreen & Strauss, 1991). As an alternate form of this test for follow-up (to partial out practice effects) the distractor items from the initial examination were used as targets.

Booklet Category Test: This test was designed to assess abstraction and concept formation, and is considered a test of executive functions. The subject is presented with 208 stimulus cards which depict a figure(s) which is supposed to represent a number from 1 to 4. The subject indicates to the examiner which number they consider to be correct and the examiner informs them whether they are correct or incorrect. Regardless of the response, the subject then proceeds to the next stimulus. The first 6 subtests have one concept which runs throughout the subtest. Thus, once the subject is able to identify the concept they can obtain correct answers for every stimulus card. The subject is informed that the concept can remain the same or change between subtests. The seventh and final subtest is a compilation of all prior subtests in order to assess the subject's memory for previous concepts. Subjects are considered impaired if they obtain 50 or more errors (Reitan & Wolfson, 1985).

Wisconsin Card Sorting Test (WCST): This is a test of executive functioning which assesses the subject's ability to form abstract concepts, and shift and maintain mental set. The subject is provided with four key cards depicting four different shapes, colours, and numbers (i.e., one red triangle, two green stars, three yellow crosses, and four blue circles). The subject is given a series of 128 cards one at a time and is

instructed to match the card in their hand to one of the four key cards. They are told whether they are correct or incorrect but they cannot change their choice. Once the subject has obtained 10 correct sorts in a row the examiner switches the correct sorting category, unbeknownst to the subject. The correct sorting categories alternate between colour, form (shape), and number sequentially. Normative data is available for adults below age 60 (Heaton, 1981).

Beck Depression Inventory (BDI): This is a self-report measure which assesses severity of depressive symptomatology. Subjects read a question or statement and choose the response (of four) that best applies to them over the last 7 days. Cut-off scores have been established for the following categories: normal, mild-moderate depression, moderate-severe depression, and extremely severe depression. Normative data are provided by the authors for six different populations: mixed diagnostic individuals, single episode major depressives, recurrent episode major depressives, dysthymic individuals, alcoholics, and heroin abusers (Beck & Steer, 1987).

Beck Hopelessness Scale (BHS): This is a self-report measure which assesses severity of hopelessness. Subjects are provided with statements to which they must respond true or false as it applies to them over the last 7 days. Cut-off scores have been established for the following categories: normal, mild hopelessness, moderate hopelessness, and severe hopelessness. Normative data are provided by the authors for seven different populations: suicide ideators, suicide attempters, alcoholics, heroin addicts, single episode major depressives, recurrent episode major depressives, and dysthymic individuals (Beck & Steer, 1988).

State-Trait Anxiety Inventory (STAI): This is a self-report measure of both situational and characterological anxiety. Subjects respond to statements which assess their symptoms of anxiety both when the subject is filling out the questionnaire, and in general. Normative data have been provided for working adults, college students, high school students, and military recruits. Age ranges from 19 to 69 (Spielberger, 1983).

Wechsler Adult Intelligence Scale-Revised (WAIS-R), Vocabulary subtest: This subtest assesses subjects' expressive vocabulary, and is considered to be a good overall estimator of premorbid intelligence. Normative data is provided for adults aged 16 to 79 years in the WAIS-R manual (Wechsler, 1981). An estimate of premorbid intelligence was derived from this measure. Krull, Scott, and Sherer (1995) suggest the following calculation: Full Scale IQ = $69.43 + .85(\text{education}) - 2.68(\text{race}) - .66(\text{occupation}) + .76(\text{Vocabulary raw score})$. The education and occupational breakdowns are provided in their publication. Based on this formula, an estimated IQ was calculated for each subject.

Raven's Standard Progressive Matrices: This is a test of visual reasoning which is used to estimate premorbid intelligence. It is considered to be less culturally-biased than verbal measures. The test is composed of 60 items grouped into five sets containing 12 items each. Each item contains a pattern with a piece missing. Subjects are required to determine which of the provided responses best completes the pattern. Normative data is provided for children and adults from a British population (Raven, 1960). North American normative data is provided by Burke (1985) and Peck (1970).

Quick Test: This is a measure of receptive vocabulary which requires the subject to point to the picture (out of an array of 4) which best depicts the word provided by the

examiner. Words become increasingly more abstract as the test progresses. Each of the three forms contain 50 words. Normative data based on the performances of 458 white children and adults is provided. Users may derive both mental age equivalents or IQ scores (Ammons & Ammons, 1962).

Expanded Disability Status Scale: A measure used by neurologists to assess the degree of disability exhibited by MS patients in specific areas of functioning (see Appendix D).

Statistical Analyses

According to Tabachnick and Fidell (1996), there are three issues that should be addressed before data analysis begins: missing data, outliers, and normality. There are a number of ways that missing data can be treated. The method used in the current study was simply to drop the cases (on a variable per variable basis) where data were missing. In most cases only one case was missing. This method was chosen over mean or regression substitution because of the small sample size. It was felt that any estimation of data may artificially diminish the degree of variance present in the sample, and in turn, decrease the likelihood of significant correlation with other variables. The data were examined and corrected for possible outliers due to incorrect data entry and failure to specify missing data codes. Again, as a result of the small sample size, and the known variability between MS patients as a whole (i.e., the population from which data was sampled), those data points that appeared to be sufficiently different from their counterparts were included in the analysis in order to better reflect the variability in the population. Lastly, although data may have, at times, departed from normality, data

transformations were considered inappropriate, again as a result of the small sample size and the potential for misrepresentation. Interpretation of the results of analyses on transformed data is difficult, thus, the clinical utility of the findings is often diminished. As the purpose of this study is, in part, to improve predictability of cognitive functioning based on organic parameters, data transformation was not performed. It should be stressed that these potential violations of assumptions, combined with the small sample size, are sufficient to demand caution when interpreting and generalizing results.

Hypothesis 1, regarding the expectation that subjects will exhibit aspects of the subcortical dementia profile, was addressed with descriptive methods. Scores for subjects on each measure were compared with the normative sample specific to the particular test in question. Average impairment ratings (AIR) were then calculated in order to reflect the degree of impairment. See below for the method for calculating the AIR.

In order to determine which particular variables should be included in the later analyses, preliminary correlational analyses were performed. Within each domain, variables were selected for further analysis if they correlated well with other variables in that domain, and if appropriate normative data (i.e., means and standard deviations) was available to allow calculation of the AIR.

The expectation that ALL will correlate significantly with EDSS ratings (hypothesis 2), and that the same MRI variable will also correlate significantly with subcortical neuropsychological variables (hypothesis 3) were tested with similar statistical procedures. First, a Pearson correlational matrix was established. For

hypothesis 2, the following variables were included in the matrix: ALL, disease duration, age, education, IQ, and EDSS score. The variables of interest are ALL, and EDSS score. The other four variables were included as control variables.

For hypothesis 3, summary scores were established for the four neuropsychological domains of interest: information processing speed, recall, executive functioning, and affective disturbance. These scores were expressed in the form of an AIR. This score represents the average value of a number of neuropsychological tests expressed in standard deviation units (Rennick, cited in Russell, Neuringer, & Goldstein, 1970). Each neuropsychological test was scored according to a 6-point scale (0-5), where 0 represents above average performance, 1 represents performance within normal limits, and 2 to 5 representing mild, moderate, severe, and very severe impairment, respectively. See Table 2 for a more detailed outline.

The format of the results of some measures did not conform well to this particular scale, thus, modifications were made for four measures. First, normative data published by Reitan and Wolfson (1985) for the Category Test provides only suggested cutoff scores rather than means and standard deviations. Additionally, they do not provide scores representative of a moderate degree of impairment. The following scale was thus utilized. An error score of 0 to 25 was considered to be above average and represented by an impairment rating of 0, 26-45 errors was considered as normal and represented by 1, 46-65 errors was considered as mildly impaired and represented by 2, and 65 or more errors was considered as severely impaired and represented by 4 (in order to more closely fit the same degree of impairment on the standard scale). Similar difficulties were

Table 2.**Impairment Rating Scale**

Impairment Rating	Standard Deviation Range	Descriptive Label
0	+1 and above	above average
1	+1 to -1	average
2	-1 to -2	mildly impaired
3	-2 to -3	moderately impaired
4	-3 to -4	severely impaired
5	-4 and below	very severely impaired

encountered when attempting to provide impairment ratings for the affective measures. The Beck scales (Beck Depression Inventory, and Beck Hopelessness Scale) were rated according to the categorizations provided in the manuals. A rating of 1 was representative of normal functioning, 2 represented mildly depressive/hopeless symptoms, 3 represented moderate symptoms, and 4 represented severe symptoms. The State-Trait Anxiety Inventory (STAI) was also graded on the same scale from normal to severe. A score between the 1st and the 75th percentile was given a rating of 1 (normal), the 76th and the 91st a rating of 2 (mildly anxious), the 92nd and the 98th a rating of 3 (moderately anxious), and above the 98th a rating of 4 (severely anxious). These latter breakdowns of percentile scores were the same values used to distinguish between average, high average, superior, and very superior on the WAIS-R, and thus, were not completely arbitrary.

The information processing speed AIR was based on scores from the Stroop Test, Trail Making test, Gordon Reaction Time test, Digit Span & Visual Span (from the WMS-R), and Consonant Trigrams. The memory score was based on scores from the CVLT and RVDLT. The executive score was based on scores from the Category Test at baseline and the WCST at follow-up. Finally, the affective disturbance score was based on the BDI, BHS, and STAI. The particular variables utilized from each measure are outlined below in the Results section. The AIR for each domain was calculated by taking the mean of all relevant standard deviation units.

The following variables were included in the correlational matrix: ALL, disease duration, age, education, IQ, information processing speed AIR, recall AIR, executive

AIR, and affective disturbance AIR. In order to determine which variables from each measure should be included in the calculation of the AIR, preliminary correlational analyses were performed. Only those variables which correlated well with other variables in the same domain, and for which appropriate normative data was available (i.e., means and standard deviations) were included in the analysis.

Opinion varies with respect to the role played by age and education in studies such as this. Prigatano & Parsons (1976) reported that age and education can significantly influence performance on neuropsychological tests; however, correlational studies which examined the relationship between MRI variables and neuropsychological variables have reported conflicting results. Some investigators have found that age and education do not play a significant role (Izquierdo et al., 1991; Tsolaki et al., 1994), whereas others have found significant relationships (Franklin et al., 1988). Still others have controlled for these effects in the statistical analysis (Pugnetti et al., 1993; Rao et al., 1989). Thus, in the current study, age and education were subjected to further analysis only if found to be significantly correlated to the variables of interest in the correlational matrix. Similar findings have been noted in the literature with respect to disease duration. Some investigators have found this variable to have a significant impact on their findings (Ron et al., 1991; Stevens et al., 1986), whereas others have found no such relationship (Frank et al., 1994; Rao et al., 1985 & 1989; Reese et al., 1986). Again, disease duration was subjected to further analysis in the current study only if found to significantly correlate with variables of interest. Finally, although IQ has received little attention in the literature, there is reason to believe that this variable may significantly influence

neuropsychological test performance (Ron et al., 1991). As such, it was also included in the correlational matrix, and subjected to further analysis if found to be significant.

Given the above, all variables found to be significantly correlated were included in a hierarchical sequential regression analysis. This type of regression allows the researcher to determine which variables are entered into the regression equation at which step of the analysis. As such, those control variables found to be significant in the correlational matrix were entered on the first step in order to partial out their effects from the variables of interest. The MRI variable (ALL) was entered on the second step. The outcome variable for hypothesis 2 was the EDSS score. In order to test hypothesis 3, separate analyses were performed for each neuropsychological outcome variable of interest: information processing AIR, recall AIR, executive AIR, and affective disturbance AIR. The regressions allowed determination of the proportion of variance in the outcome variables accounted for by each of the predictor variables.

Lastly, hypothesis 4 proposed that a significant relationship would be found between the change in TLL over time and the change in neuropsychological performance over time. The neuropsychological variable(s) included in this analysis depended on which of these variables appeared to be the most significant in the above analyses. Once this was established, difference scores were calculated between baseline and follow-up for TLL, and the relevant neuropsychological variable(s). In turn, a correlational analysis determined whether the change in MRI variables was indeed related to the change in neuropsychological performance over time.

CHAPTER 7

RESULTS

Subcortical Dementia Profile

The expectation that subjects would demonstrate aspects of the subcortical dementia profile (Hypothesis 1) was addressed by examining the AIRs of each variable. For each variable of interest, subjects were assigned an impairment rating according to the scale discussed above. Each rating was reflective of that particular subject's performance relative to the mean and standard deviation indicated for that particular test. Where possible, age matched normative data was utilized. The mean of all subjects' ratings was then calculated. This value was the AIR. The AIR values for each variable are listed in Table 3 (baseline data) and Table 4 (follow-up data). The variables listed were selected according to criteria outlined below in the Preliminary Analyses section.

In general, performance of this population of individuals with relapsing-remitting MS on measures of so-called "subcortical" functioning ranged from average to mildly impaired, as reflected by the AIRs across subjects for each test of interest. The majority of the ratings were reflective of performance between one standard deviation above to two standard deviations below the normative mean for each particular measure. At both baseline and follow-up performance in all domains of functioning appeared to be comparable. The mean of all AIRs across subjects was calculated for each functional domain. The mean AIR for attentional measures was 1.465 at baseline and 1.488 at follow-up. For the memory measures the mean AIR was 1.455 at baseline and 1.259 at follow-up. In the executive domain the mean AIR at baseline was 1.677, and 1.217 at

Table 3.**Average Impairment Ratings Across Subjects for Measures of "Subcortical" Functioning at Baseline**

Variable Description	AIR	Variable Description	AIR
Consonant Trigrams 9sec delay	1.917 a	CVLT Short Delay Cued Recall	1.364 m
Consonant Trigrams 18sec delay	1.750 a	CVLT Short Delay Free Recall	1.364 m
Digit Span Backwards	1.167 a	CVLT Trial 5	1.545 m
Gordon Vigilance Commissions	1.250 a	CVLT List B	1.091 m
Gordon Vigilance Latency	1.417 a	RVDLT Trial 5	1.417 m
Gordon Vigilance Total Correct	1.583 a	RVDLT Recognition	2.167 m
Modified Stroop Color/Word-ColorTime	1.167 a	RVDLT Total Correct	1.417 m
Modified Stroop Color Time	1.833 a	Category Test Total Errors	1.667 e
Modified Stroop Color/Word Time	1.333 a	Modified Stroop Mental Shifting	1.455 e
Stroop Color	1.667 a	Trail Making Part B Time	1.909 e
Stroop Word	1.333 a	Beck Depression Inventory	1.333 f
Stroop Word/Color	1.167 a	Beck Hopelessness Scale	1.500 f
CVLT Long Delay Cued Recall	1.273 m	STAI State Anxiety	1.455 f
CVLT Long Delay Free Recall	1.455 m	STAI Trait Anxiety	1.636 f

a=attention/information processing measure

m=memory measure

e=executive measure

f=affect measure

(see Table 2 for range of values)

Table 4.

Average Impairment Ratings Across Subjects for Measures of "Subcortical" Functioning at Follow-up

Variable Description	AIR	Variable Description	AIR
Consonant Trigrams 9sec delay	2.083 a	CVLT Short Delay Cued Recall	1.083 m
Consonant Trigrams 18sec delay	1.833 a	CVLT Short Delay Free Recall	1.167 m
Digit Span Backwards	1.083 a	CVLT Trial 5	1.500 m
Gordon Vigilance Commissions	1.000 a	CVLT List B	1.500 m
Gordon Vigilance Latency	1.667 a	RVDLT Trial 5	1.083 m
Gordon Vigilance Total Correct	1.500 a	RVDLT Recognition	1.500 m
Modified Stroop Color/Word-ColorTime	1.222 a	RVDLT Total Correct	0.917 m
Modified Stroop Color Time	1.667 a	Modified Stroop Mental Shifting	1.111 e
Modified Stroop Color/Word Time	1.222 a	Trail Making Part B Time	1.667 e
Stroop Color	1.583 a	WCST Perseverative Errors	1.000 e
Stroop Word	1.500 a	WCST Perseverative Responses	1.091 e
Stroop Word/Color	1.500 a	Beck Depression Inventory	1.667 f
CVLT Long Delay Cued Recall	1.167 m	Beck Hopelessness Scale	2.000 f
CVLT Long Delay Free Recall	1.417 m	STAI State Anxiety	1.625 f
		STAI Trait Anxiety	2.000 f

a=attention/information processing measure

m=memory measure

e=executive measure

f=affect measure

follow-up. The mean AIR for affect was 1.481 at baseline and 1.823 at follow-up. The significance of any changes in these AIR scores for each functional domain is addressed below with t-tests when discussing the results of hypothesis 4.

A Pearson correlational analysis was performed on all neuropsychological domains of interest (i.e., attention AIR, memory AIR, executive AIR, affect AIR) in order to determine if they were interrelated. Results revealed significant relationships between the three cognitive variables, whereas the variable representing emotional functioning (i.e., affect) did not correlate significantly with the other three. At baseline, the attention AIR ($M = 1.4653$, $SD = .4571$) and the memory AIR ($M = 1.5090$, $SD = .9514$) were positively related ($r = .8379$, $p = .001$), the attention AIR and the executive AIR ($M = 1.6806$, $p = .8241$) were positively related ($r = .7087$, $p = .010$), and the memory AIR and the executive AIR were positively related ($r = .7289$, $p = .007$). At follow-up, the attention AIR ($M = 1.5017$, $SD = .3449$) and the memory AIR ($M = 1.2593$, $SD = .7703$) were positively related ($r = .6614$, $p = .019$), the attention AIR and the executive AIR ($M = 1.2642$, $SD = .5069$) were positively related ($r = .7437$, $p = .006$), and the memory AIR and the executive AIR were positively related ($r = .7909$, $p = .002$).

IQ Calculation

As discussed above, IQ was included as a potentially contributing factor in analyses which addressed Hypotheses 2 and 3. Although several measures of IQ functioning were administered (i.e., Raven's Progressive Matrices, Quick Test, WAIS-R Vocabulary), it was decided that the outcome of only one measure would be included in the analysis. Preliminary correlational analyses between variables representing all three

IQ measures revealed that the Raven's Progressive Matrices did not correlate with either the Quick Test or the WAIS-R Vocabulary measure. Results from the Raven's, based on three different normative data sets, were calculated (see Instruments and Measures section), but none of the three correlated with the other IQ measures. Given that the Ravens test did not appear to measure the same factor, it was excluded from further analyses. However, this preliminary analysis did reveal a significant correlation between the Quick Test and the Vocabulary IQ estimate. The correlation was of such magnitude ($r = .91$, $p = .002$) that it was decided that only one measure would be necessary, because only a negligible amount of extra variance would be accounted for by the inclusion of both measures. Given that only 10 subjects completed the Quick Test (two subjects were French speaking and a French translation of the test was unavailable), and all 12 completed the Vocabulary subtest, it was decided that only the Vocabulary IQ estimate would be included in further analyses. The correlational matrix for the IQ measures is presented in Table 5.

Preliminary Correlational Analyses

In order to decide which neuropsychological variables should be included in the calculation of the average impairment ratings (AIRs) preliminary correlational analyses of the baseline data were performed for each domain of interest. With respect to the attention (or information processing speed) domain, results of the following tests were included in this analysis: Consonant Trigrams, Digit Span (forward and backward), Visual Span (forward and backward), Gordon Diagnostic System (GDS; Vigilance and Distractibility subtests), Stroop Test, and the Trail Making Test (Part A). Only those

Table 5.
Pearson Correlational Matrix of IQ Measures

	Quick Test IQ	Vocabulary IQ estimate	Raven's British norms	Raven's Burke norms	Raven's Peck norms
Quick Test IQ	1.00	.9100 p=.002	.3282 p=.427	.3826 p=.350	.3205 p=.439
Vocabulary IQ estimate		1.00	.3627 p=.273	.3918 p=.233	.3625 p=.273
Raven's British norms			1.00	.8753 p=.000	.8784 p=.000
Raven's Burke norms				1.00	.9950 p=.000
Raven's Peck norms					1.00

tests that significantly correlated with other attentional measures, and those for which appropriate normative data were available (i.e., means and standard deviations from a "normal" population), were considered for further analysis. A correlational matrix of the selected attentional variables is presented in Table 6.

At baseline, the Category test was administered as a measure of executive functioning, with the Wisconsin Card Sorting Test (WCST) being administered at follow-up. Other measures which, clinically, are also considered to tap executive abilities are the Trail Making Test (Part B), and one subtest of the modified Stroop test, both of which require the subject to switch mental set. Some doubt exists regarding the correlation between the Category Test and the WCST. However, the inclusion of both of these measures in the preliminary correlational analysis of executive measures demonstrates that in this subject population, the tests can be considered to tap at least some of the same abilities, given the significance of the correlations between the total number of errors on the Category test and the number of perseverative responses on the WCST ($r = .6633$, $p = .026$). A correlational matrix of the selected executive measures is presented in Table 7. The WCST variables are representative of results at follow-up, whereas all other variables are from the baseline data. The Raven's Progressive Matrices results did not correlate significantly with the WCST, and thus, was not considered as an executive measure.

With respect to the memory domain, both the California Verbal Learning Test (CVLT) and the Rey Visual Design Learning Test (RVDLT) were administered. Once again, those variables which correlated well with other memory variables, and for which appropriate normative data (i.e., means and standard deviations) was available, were

Table 7.

Pearson Correlational Matrix of Executive Measures

	Category total errors	Modified Stroop mental shifting	Trails B total time	WCST perseverative errors	WCST perseverative responses
Category total errors	1.0000	.3206 p=.336	.7877 p=.004	.5132 p=.106	.6633 p=.026
Modified Stroop mental shifting		1.0000	.6875 p=.028	.6316 p=.050	.7157 p=.020
Trails B total time			1.0000	.6112 p=.060	.7101 p=.019
WCST perseverative errors				1.0000	.9393 p=.000
WCST perseverative responses					1.0000

included in further analyses. The selected memory variables are presented in Table 8.

In the affective domain, the following tests were administered: Beck Depression Inventory (BDI), Beck Hopelessness Scale (BHS), and State-Trait Anxiety Inventory (STAI). All three tests were intercorrelated, and therefore were used in future analyses. A correlational matrix of the affective variables can be found in Table 9. Some might argue that the BDI is inappropriate for use with a physically disabled population given that some of the items would be endorsed due to physical problems unrelated to depression. These somatic complaints are represented on page 2 of the questionnaire. A correlational analysis comparing results from page 1 with page 2 revealed that the two sides were significantly correlated ($r = .6988$, $p = .011$). These results suggest that physical complaints were not likely to contribute significantly to the findings, and thus, the use of the total BDI score was appropriate in this case.

Expanded Disability Status Scale

Hypothesis 2 stated that ALL would be positively correlated with the degree of disability as documented on the EDSS at both baseline and follow-up. Pearson correlation coefficients were calculated between ALL and EDSS, as well as between the following control variables: disease duration (from both year of symptom onset and year of diagnosis), age, education, and IQ. The relationship between ALL and EDSS was found to be non-significant at both baseline ($r = .2703$, $p = .396$), and follow-up ($r = -.2142$, $p = .504$). The only significant correlations for the variables of interest were as follows: ALL was negatively correlated with education level at baseline ($r = -.5889$, $p = .044$), such that active lesions decreased with increasing educational

Table 9.

Pearson Correlational Matrix of Affect Measures

	BDI Category	BHS Category	STAI State score	STAI Trait score
BDI Category	1.000	.6211 p=.031	.6294 p=.038	.4685 p=.146
BHS Category		1.000	.7180 p=.013	.6172 p=.043
STAI State Score			1.000	.5500 p=.100
STAI Trait Score				1.000

attainment, and EDSS was positively correlated with age at baseline ($r = .5817$, $p = .047$), such that degree of disability increased with increasing age. No significant correlations for the variables of interest (i.e., ALL and EDSS) were found at follow-up.

In order to determine if the lack of correlation between ALL and EDSS was due to the fact that EDSS was a summary score of various types of disability (thereby potentially overlooking correlations with a specific kind of disability), a correlational matrix was calculated between ALL and the subscales of the EDSS. Subscales representing functions subserved by the following areas were considered: pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual, cerebral (or mental), and "other." No significant results were obtained. However, it is interesting to note that the only correlation that approached significance was that between ALL and cerebral (or mental) functions at baseline ($r = .5404$, $p = .070$).

The correlations between the MRI variable ALL and EDSS (cerebral/mental subscale) were repeated substituting TLL (or burden of disease) for ALL. This was done in order to determine whether the T2 MRI variable was more likely to be related to disability than simply the active lesions detected by gadolinium on T1 MRI images. This too yielded non-significant correlations at both baseline ($r = .2550$, $p = .424$) and follow-up ($r = -.1145$, $p = .723$).

Attention and Information Processing Speed

Pearson correlation coefficients were calculated for the relationship between ALL and the attention AIR. The following control variables were also included: age, education, disease duration (since onset and diagnosis), and IQ. The relationship between

ALL ($\underline{M} = 1.2500$, $SD = 1.6026$) and the attention AIR ($\underline{M} = 1.4653$, $SD = .4571$) at baseline, was found to be non-significant ($r = .0026$, $p = .994$). However, the attention AIR was positively correlated with disease duration since diagnosis ($\underline{M} = 2.7500$, $SD = 2.8959$) at baseline ($r = .7197$, $p = .008$), indicating that the longer the duration of disease, the greater the attentional impairment.

At follow-up, results again revealed a non-significant relationship ($r = .5230$, $p = .081$) between ALL ($\underline{M} = 1.5000$, $SD = 2.7136$) and the attention AIR ($\underline{M} = 1.5017$, $SD = .3449$). Once again, the attention AIR was positively correlated with disease duration since diagnosis at follow-up ($r = .6331$, $p = .027$). However, contrary to the results at baseline, the attention AIR was also positively correlated with education ($\underline{M} = 3.0833$, $SD = 1.0836$) at follow-up ($r = .6272$, $p = .029$), suggesting that individuals with more education demonstrated more severe attentional impairments.

Because it is the purpose of this study to examine potential relationships between organic pathology (as documented on MRI) and cognitive variables (as documented by neuropsychological testing), it was important to examine if cognitive findings were related to the other MRI variable of interest; namely, TLL or burden of disease (although this relationship was not hypothesized). As such, the above correlational analyses were repeated, substituting TLL for ALL. This analysis yielded significant results, such that, at baseline, TLL ($\underline{M} = 2491.0417$, $SD = 2531.3400$) and the attention AIR were significantly and positively correlated ($r = .5915$, $p = .043$), indicating that individuals with more disease burden exhibited more compromise with respect to their attentional abilities. The same significant relationship was demonstrated at follow-up. TLL ($\underline{M} =$

2650.2000, $SD = 2633.9968$) was positively correlated with attention AIR ($r = .6395$, $p = .025$).

Given the significance of the relationships between the attention AIR, TLL, and disease duration (since diagnosis) at baseline, and those variables plus the additional education variable at follow-up, they were subjected to multivariate regression analyses. Thus, a hierarchical (sequential) multiple regression (i.e., a regression for which the researcher decides the order of entry into the regression equation), was employed to determine if the addition of TLL improved the prediction of the Attention AIR beyond that afforded by disease duration (since diagnosis). Analysis was performed using SPSS REGRESSION.

Table 10 displays the correlations between the variables, the unstandardized regression coefficients (B) and intercept, the standardized regression coefficients (β), the semipartial correlations (sr^2), and R , R^2 , and adjusted R^2 after entry of both independent variables. R was significantly different from zero at the end of step one only. After step 2, with both independent variables in the equation, $R = .73$, $F(2, 9) = 5.1238$, $p = .0327$.

After step 1, with disease duration (since diagnosis) in the equation, $R^2 = .52$, $F(1, 10) = 10.747$, $p = .008$. After step 2, with TLL added to the prediction of the Attention AIR, $R^2 = .53$, $F(2, 9) = 0.277$, $p = .611$. Examination of the significance levels for the semipartial correlation coefficients in Table 10 shows that the addition of TLL to the equation with disease duration did not result in a significant increment in R^2 .

These findings demonstrate that 52% (47% adjusted) of the variability in the attention AIR at baseline was predicted by disease duration, and that TLL did not add a

Table 10.

Hierarchical Multiple Regression of Disease Duration and Total Lesion Load on the Average Impairment Rating for Attention at Baseline

Variables	Attention AIR (dep. variable)	Disease Duration	Total Lesion Load (TLL)	B	β	sr^2
Attention AIR	1	.720 (p = .004)	.591 (p = .021)			
Disease Duration	.720 (p = .004)	1	.703 (p = .005)	0.095	0.601	0.52 (p = .008)
TLL	.591 (p = .021)	.703 (p = .005)	1	<.0001	0.169	0.01 (p = .611)
Means	1.465	2.75	2491.042			
Standard deviations	0.457	2.896	2531.34			

Intercept = 1.1285

$R^2 = .53$

Adjusted $R^2 = .43$

Multiple R = .73

significant amount of further variance.

According to statistical tradition, control variables are entered first into regression equations. However, there is reason to question this practice here. Given that disease duration is a measurement that can be influenced by many factors (i.e., time delay following onset of symptoms after which patient presents to physician, availability of physician experienced at diagnosing MS, physician bias in interpreting diagnostic criteria, waiting periods for test results, etc...), the reliability of this variable is questionable. In the literature, MRI findings have been demonstrated to be reliable predictors of actual pathology. As such, the analysis was repeated entering TLL on the first step and disease duration on the second. Here, TLL did indeed significantly predict Attention AIR and disease duration did not add any further variance. Overall predictability remains constant. See Table 11 for the results. After step 1, with TLL in the equation, $R^2 = .35$, $F(1, 10) = 5.380$, $p = .043$. After step 2, with disease duration added to the prediction of the Attention AIR, $R^2 = .53$, $F(2, 9) = 3.51$, $p = .094$. Examination of the significance levels for the semipartial correlation coefficients in Table 11 shows that the addition of disease duration to the equation with TLL did not result in a significant increment in R^2 .

These findings demonstrate that 35% (28% adjusted) of the variability in the attention AIR at baseline was predicted by TLL, and that disease duration did not add a significant amount of further variance.

For the follow-up data, another hierarchical (sequential) multiple regression analysis was employed to determine if the addition of disease duration (since diagnosis) and TLL improved the prediction of the Attention AIR beyond that afforded by

Table 11.

Hierarchical Multiple Regression of Total Lesion Load and Disease Duration on the Average Impairment Rating for Attention at Baseline

Variables	Attention AIR (dep. variable)	Total Lesion Load (TLL)	Disease Duration	B	β	sr^2
Attention AIR	1	.591 (p = .021)	.720 (p = .004)			
TLL	.591 (p = .021)	1	.703 (p = .005)	<.0001	0.169	0.35 (p = .043)
Disease Duration	.720 (p = .004)	.703 (p = .005)	1	0.095	0.601	0.18 (p = .094)
Means	1.465	2491.042	2.75			
Standard deviations	0.457	2531.34	2.896			

Intercept = 1.1285

$R^2 = .53$

Adjusted $R^2 = .43$

Multiple R = .73

education. Education was converted to a continuous variable for the purposes of this analysis.

Table 12 displays the correlations between the variables, the unstandardized regression coefficients (B) and intercept, the standardized regression coefficients (β), the semipartial correlations (sr^2), and R , R^2 , and adjusted R^2 after entry of all three independent variables. R was significantly different from zero at the end of step 1 (education) only. After step 3 with all independent variables in the equation, $R = .78$, $F(3, 8) = 4.0350$, $p = .0509$.

After step 1, with education in the equation, $R^2 = .39$, $F(1, 10) = 6.4855$, $p = .029$. After step 2, with disease duration added to the prediction of the AttentionAIR, $R^2 = .56$, $F(2, 9) = 3.469$, $p = .095$. After step 3, with TLL added to the prediction of the Attention AIR, $R^2 = .60$, $F(3, 8) = 0.802$, $p = .396$. Examination of the significance levels for the semipartial correlation coefficients in Table 12 shows that the addition of disease duration and TLL to the equation with education did not result in a significant increment in R^2 .

These findings demonstrate that 39% (33% adjusted) of the variability in the attention AIR at follow-up was predicted by education, and that disease duration, and TLL did not add a significant amount of further variance.

As with the baseline analysis, the follow-up regression was re-done entering TLL on the first step. TLL did significantly predict Attention AIR and the control variables added no further variance. Overall predictability remained constant. See Table 13 for the results.

After step 1, with TLL in the equation, $R^2 = .41$, $F(1, 10) = 6.918$, $p = .025$. After

Table 12.

Hierarchical Multiple Regression of Education, Disease Duration, and Total Lesion Load on the Average Impairment Rating for Attention at Follow-up

Variables	Attention AIR (dep. variable)	Educ	Disease Duration	Total Lesion Load (TLL)	B	β	sr^2
Attention AIR	1	.627 (p = .015)	.633 (p = .014)	.639 (p = .013)			
Educ	.627 (p = .015)	1	.413 (p = .091)	.380 (p = .111)	0.066	0.416	0.39 (p = .029)
Disease Duration	.633 (p = .014)	.413 (p = .091)	1	.760 (p = .002)	0.027	0.226	0.17 (p = .095)
TLL	.639 (p = .013)	.380 (p = .111)	0.760 (p = .002)	1	<.0001	0.309	0.04 (p = .396)
Means	1.502	14.167	2.75	2650.2			
Standard deviations	0.345	2.167	2.896	2633.997			

Intercept = 0.3822

$R^2 = .60$

Adjusted $R^2 = .45$

Multiple R = .78

Table 13.

Hierarchical Multiple Regression of Total Lesion Load, Education, and Disease Duration on the Average Impairment Rating for Attention at Follow-up

Variables	Attention AIR (dep. variable)	Total Lesion Load (TLL)	Educ	Disease Duration	B	β	sr^2
Attention AIR	1	.639 (p = .013)	.627 (p = .015)	.633 (p = .014)			
TLL	.639 (p = .013)	1	.380 (p = .111)	.760 (p = .002)	<.0001	0.309	0.41 (p = .025)
Educ	.627 (p = .015)	.380 (p = .111)	1	.413 (p = .091)	0.066	0.416	0.17 (p = .086)
Disease Duration	.633 (p = .014)	.760 (p = .002)	0.413 (p = .091)	1	0.027	0.226	0.02 (p = .536)
Means	1.502	2650.2	14.167	2.75			
Standard deviations	0.345	2633.997	2.167	2.896			

Intercept = 0.3822

$R^2 = .60$

Adjusted $R^2 = .45$

Multiple R = .78

step 2, with education added to the prediction of the Attention AIR, $R^2 = .58$, $F(2, 9) = 3.705$, $p = .086$. After step 3, with disease duration added to the prediction of the Attention AIR, $R^2 = .60$, $F(3, 8) = 0.418$, $p = .536$. Examination of the significance value of the semipartial correlation coefficients reported in Table 13 shows that the addition of education and disease duration with TLL did not result in a significant increment in R^2 .

These findings demonstrate that 41% (35% adjusted) of the variability in the attention AIR at follow-up was predicted by TLL, and that education and disease duration did not add a significant amount of further variance.

Memory

Pearson correlation coefficients were calculated between ALL and the memory AIR. The control variables discussed above in the attention section were also included in the analysis. The baseline relationship between ALL and the memory AIR ($M = 1.5090$, $SD = .9514$) was non-significant ($r = .0814$, $p = .801$). At follow-up, the relationship between ALL ($M = 1.5000$, $SD = 2.7136$) and the memory AIR ($M = 1.2593$, $SD = .7703$) was also non-significant ($r = .0677$, $p = .835$).

As above for attention, the analyses were repeated substituting TLL for ALL. A significant positive correlation was found between TLL ($M = 2491.0417$, $SD = 2531.3400$) and the memory AIR ($r = .6141$, $p = .034$) at baseline, suggesting that greater burden of disease was associated with corresponding decreases in memory functioning. However, contrary to the baseline results, at follow-up the relationship between TLL ($M = 2650.2000$, $SD = 2633.9968$) and the memory AIR was not significant ($r = .3919$, $p =$

.208).

As a result of the insignificant findings at follow-up, further analyses were performed on baseline data only. Given the lack of significant correlations between the memory AIR and the control variables, a bivariate regression analysis was performed in lieu of multiple regression. Thus, a standard bivariate regression was performed on the baseline data between the memory AIR as the dependent variable and TLL as the independent variable. Analysis was performed using SPSS REGRESSION.

Table 14 displays the correlations between the variables, the unstandardized regression coefficients (B) and intercept, the standardized regression coefficients (β), R, R^2 , and adjusted R^2 . R for regression was significantly different from zero, $F(1, 10) = 6.0531$, $p = .0337$.

These findings demonstrate that 38% (31% adjusted) of the variability in the memory AIR at baseline was predicted by TLL or burden of disease (mm^3).

Executive Functions

Pearson correlation coefficients were calculated, for baseline data, between ALL and the executive AIR ($M = 1.6806$, $SD = .8241$), as well as the control variables. The relationship between the two variables of interest was non-significant ($r = .0774$, $p = .811$), nor was any relationship found between the executive AIR and control variables. The same pattern of results was found at follow-up. ALL was not significantly correlated ($r = .4134$, $p = .182$) with the executive AIR ($M = 1.2642$, $SD = .5069$), nor were the control variables correlated with the executive AIR.

As above, the analyses were repeated substituting TLL for ALL. The baseline

Table 14.

Standard Bivariate Regression of Total Lesion Load on the Average Impairment Rating for Memory at Baseline

Variables	Memory AIR (dep. variable)	Total Lesion Load (TLL)	B	β
Memory AIR	1	.614 (p = .017)		
TLL	.614 (p = .017)	1	0.0002	0.614
Means	1.51	2491.04		
Standard deviations	0.95	2531.34		

Intercept = .934

$R^2 = .38$

Adjusted $R^2 = .31$

Multiple R = .61

analysis yielded a significant positive relationship ($r = .6665$, $p = .018$) between TLL ($M = 2491.0417$, $SD = 2531.3400$) and the executive AIR. The same significant positive relationship was documented at follow-up. TLL ($M = 2650.2000$, $SD = 2633.9968$) was correlated with the executive AIR ($r = .6993$, $p = .011$).

Due to the lack of significant correlations between the executive AIR and the control variables at both baseline and follow-up, bivariate regression analyses were performed in lieu of multiple regression. A standard bivariate regression was performed between the executive AIR as the dependent variable and TLL as the independent variable.

Table 15 displays the correlation between the variables, the unstandardized regression coefficients (B) and intercept, the standardized regression coefficients (β), R , R^2 , and adjusted R^2 for the baseline data. R for regression was significantly different from zero, $F(1, 10) = 7.9940$, $p = .0179$.

These findings demonstrate that 44% (39% adjusted) of the variance in the executive AIR at baseline was predicted by TLL or burden of disease (mm^2) at baseline.

The same standard bivariate regression analysis was repeated using the follow-up data with the executive AIR as the dependent variable and the TLL as the independent variable. Table 16 displays the same values as above. R for regression was significantly different from zero, $F(1, 10) = 9.5713$, $p = .011$.

These findings demonstrate that 49% (44% adjusted) of the variability in the executive AIR at follow-up was predicted by TLL or burden of disease (mm^2).

Table 15.

Standard Bivariate Regression of Total Lesion Load on the Average Impairment Rating for Executive Functions at Baseline

Variables	Executive AIR (dep. variable)	Total Lesion Load (TLL)	B	β
Executive AIR	1	0.667 (p = .009)		
TLL	0.667 (p = .009)	1	0.000217	0.666
Means	1.681	2491.042		
Standard deviations	0.824	2531.34		

Intercept = 1.140

$R^2 = .44$

Adjusted $R^2 = .39$

Multiple R = .67

Table 16.

Standard Bivariate Regression of Total Lesion Load on the Average Impairment Rating for Executive Functions at Follow-up

Variables	Executive AIR (dep. variable)	Total Lesion Load (TLL)	B	β
Executive AIR	1	.699 (p = .006)		
TLL	.699 (p = .006)	1	0.00013458	0.699
Means	1.26	2650.2		
Standard deviations	0.51	2633.99		

Intercept = .907

$R^2 = .49$

Adjusted $R^2 = .44$

Multiple R = .70

Affect

At baseline, Pearson correlation coefficients were calculated between ALL and the affect AIR ($M = 1.4858$, $p = .6783$), as well as the control variables. ALL was not significantly related to the affect AIR ($r = .1708$, $p = .596$). However, the affect AIR was significantly correlated with the education control variable ($M = 3.0833$, $SD = 1.0836$). The correlation was negative ($r = -.5956$, $p = .041$), such that subjects with higher educational attainment were less depressed than people with lower educational attainment. At follow-up, results again revealed a non-significant relationship ($r = -.1435$, $p = .692$) between ALL and the affect AIR ($M = 1.8000$, $SD = .8148$). However, at follow-up, education was no longer significantly related to affect.

The substitution of TLL for ALL in the above analyses did not yield any significant findings. TLL ($M = 2491.0417$, $SD = 2531.3400$) and the affect AIR were not correlated ($r = -.2191$, $p = .494$) at baseline. At follow-up, TLL ($M = 2650.2000$, $SD = 2633.9968$) and the affect AIR again did not correlate significantly. Thus, the affect AIR did not appear to be correlated with the organic pathological variables of interest.

In order to determine if affect was more closely related to environmental variables, the affect AIR was subjected to further analysis. The potential relationship between affect and perceived social support was examined. Social support was coded as being perceived as present or not from the following sources: parents and relatives, children, friends, religious organizations, secular organizations (e.g., MS Society), health care professionals, and any other source indicated by the patient. These correlational analyses also yielded non-significant results at both baseline and follow-up, such that

affect did not appear to be related to the patient's subjective ratings of available social support.

The impact of a demographic variable was also examined. Specifically, two analyses of variance were performed in order to determine whether or not occupational status had an impact on affect. The first analysis examined whether there was any significant difference between the affect AIR means for those subjects who were employed versus those who were unemployed (at baseline only). Results were nonsignificant. Occupational status was broken down further into the following groups: unemployed, on disability benefits, blue collar occupations, and white collar occupations. Once again, the analysis was nonsignificant, suggesting that there were no significant differences in affect scores between subjects falling into any of the above occupational categories.

At follow-up, affect was significantly related to the number of clinical exacerbations (that occurred between baseline and follow-up) such that as the number of exacerbations increased, so too did affective disturbance ($r = .80$, $p = .005$).

Change Over Time

Hypothesis 4 predicted that the change in TLL would be correlated with the change in subcortical neuropsychological variables over time (i.e., between baseline and 6-month follow-up). Difference scores were calculated for TLL and the neuropsychological variables of interest (i.e., attention AIR, memory AIR, executive AIR, and affect AIR). Pearson correlational analyses were then performed between difference scores for TLL and the four neuropsychological variables. All four analyses

yielded non-significant results. Thus, the change in burden of disease was not significantly related to the change in the degree of neuropsychological impairment.

In order to determine whether or not change actually did take place over time in the variables of interest, t-tests examining the difference between means (for correlated groups) were performed. Results revealed that there were no significant differences between burden of disease at baseline and follow-up. Thus, the total amount of demyelination associated with MS did not change significantly in the group as a whole. Similarly, no significant differences between results at baseline and follow-up were observed with respect to impairment of attention and memory. The degree of affective disturbance, also did not change significantly over time. The only area of impairment noted to be significantly different between baseline and follow-up was executive functioning, $t(11) = 3.22$, $p = .008$. Perusal of the means on both occasions revealed that the degree of executive impairment was greater at baseline ($M = 1.68$) than at follow-up ($M = 1.26$), such that some improvement in executive functioning occurred over time. However, given that different measures were used to tap executive abilities at baseline and at follow-up, these findings should be interpreted with caution.

Test-Retest Reliability

With the exception of a slight improvement in executive functioning, no significant changes in neuropsychological test performance occurred over time, such that attention and memory functioning appeared to remain relatively stable. This stability of cognitive status is consistent with the lack of changes in pathology documented by MRI. Thus, any minor fluctuations in test scores could potentially reflect the test-retest

reliability of the measures. In order to explore this further, Pearson correlation coefficients were calculated between the AIR scores at baseline and follow-up for all functional domains assessed, with the exception of executive functioning. The Pearson coefficient is the statistic, recommended by Anastasi (1988), that best reflects test-retest reliability. Given that different executive measures were used at baseline and follow-up, the correlation merely reflects the relationship between the two sets of measures, rather than test-retest reliability per se.

In the attention domain, the AIR scores at baseline and follow-up yielded the following relationship, $r = .80$, $p = .002$. Higher test-retest reliability was noted for the memory measures ($r = .89$, $p < .001$). The relationship between the group of executive measures at baseline and follow-up was as follows, $r = .88$, $p < .001$. The pattern of subject responding on measures of affect differed over time (although mean values were not significantly different), reflecting state changes in emotional distress. As such, no significant correlation was found ($r = .00$, $p = 1.00$), suggesting no *linear* relationship between affect at baseline and at follow-up.

In order to determine which particular measures utilized were the most stable over time, test-retest reliability was calculated for all measures administered on the two occasions. Alternate-form reliability was calculated for the California Verbal Learning Test, and the Rey Visual Design Learning Test, as different versions of these measures were used at baseline and follow-up. The Pearson correlation coefficients for all measures are included in Table 17.

Table 17.**Test-Retest and Alternate-Form Reliability**

Variable Description	r	Variable Description	r
Consonant Trigrams 9sec delay	0.82a p = .001	CVLT Short Delay Cued Recall	0.81m p = .002
Consonant Trigrams 18sec delay	0.46a p = .133	CVLT Short Delay Free Recall	0.93m p < .001
Digit Span Backwards	0.80a p = .002	CVLT Trial 5	0.78m p = .005
Gordon Vigilance Commissions	-0.20a p = .536	CVLT List B	0.51m p = .112
Gordon Vigilance Latency	0.59a p = .044	RVDLT Trial 5	0.88m p < .001
Gordon Vigilance Total Correct	-0.02a p = .936	RVDLT Recognition	0.78m p = .003
Modified Stroop Color/Word-Color Time	0.73a p = .025	RVDLT Total Correct	0.84m p = .001
Modified Stroop Color Time	0.89a p = .001	Modified Stroop Mental Shifting	0.92e p = .001
Modified Stroop Color/Word Time	0.77a p = .016	Trail Making Part B Time	0.82e p = .002
Stroop Color	0.86a p < .001	Beck Depression Inventory	0.36f p = .345
Stroop Word	0.89a p < .001	Beck Hopelessness Scale	0.73f p = .016
Stroop Word/Color	0.68a p = .016	STAI State Anxiety	-0.10f p = .811
CVLT Long Delay Cued Recall	0.86m p = .001	STAI Trait Anxiety	0.52f p = .233
CVLT Long Delay Free Recall	0.84m p = .001		

a = attention/information processing measure

m = memory measure

e = executive measure

f = affect measure

Power Analyses

In order to determine the probability that the null hypotheses were correctly rejected, power analyses were conducted. The three variables found to be significant in the correlational analyses were included in these calculations. Total lesion load (the primary variable of interest) along with disease duration and education (control variables) were considered. Given that TLL correlated with several neuropsychological outcome measures, a mean Pearson correlation coefficient was calculated in order to reflect a global power estimate. Disease duration correlated significantly with the attention outcome measure at both baseline and follow-up. The mean of these two values was used to calculate power. Education correlated significantly with only the attention outcome measure at follow-up, so the Pearson correlation coefficient from that analysis was used. Table 18 shows the calculated power values for each of these variables, as found in the power tables provided by Cohen (1988).

Table 18.**Power Analyses**

Total Lesion Load	Disease Duration	Education
TLL and ... Attention AIR (b): $r = .59$ Attention AIR (f): $r = .64$ Memory AIR (b): $r = .61$ Executive AIR (b): $r = .67$ Executive AIR (f): $r = .70$ mean $r = .64$ n = 12 a = .05 two-tailed from Cohen (1988), p.92 power = .66	Disease Duration and ... Attention AIR (b): $r = .72$ Attention AIR (f): $r = .63$ mean $r = .68$ n = 12 a = .05 two-tailed from Cohen (1988), p.92 power = .74	Education and ... Attention AIR (f): $r = .63$ $r = .63$ n = 12 a = .05 two-tailed from Cohen (1988), p.92 power = .64

b = baseline

f = follow-up

CHAPTER 8

DISCUSSION

Subcortical Dementia Profile

The initial hypothesis of this investigation was that subjects would demonstrate at least one or more aspects of the subcortical dementia profile first espoused by Cummings and Benson (1984), including: slowed information processing, forgetfulness, decreased cognition or executive functioning, and/or affective disturbance. To reiterate what was said earlier, the term “subcortical dementia” does not necessarily reflect only subcortical involvement, nor does it imply that all individuals with this profile of deficits are impaired enough to be considered demented by standard criteria. The term is considered to be a clinical, rather than an anatomical concept, and is used here only because it has become recognized universally as indicative of a particular pattern of deficits.

In the past, researchers often tested only one facet of the profile, such that adequate assessment of whether or not MS patients exhibited the profile from a global point of view was not, as yet, considered. The present study evaluated subjects, using several measures, with respect to each of the four areas of functioning. Results confirmed the original hypothesis, in that subjects did exhibit decrements in each of the areas expected. Mild deficits were documented in each of the four areas in turn, that have been documented by other authors in the past: slowed information processing or diminished attention (Beatty et al., 1988; Feinstein et al., 1993; Heaton et al., 1985; Kujala et al., 1994 & 1995; Litvan et al., 1988; Rao et al., 1989), forgetfulness and memory difficulties (D’Esposito et al., 1996; Fischer, 1988; Grant et al., 1984; Litvan et al., 1988; Minden et

al., 1990; Rao et al., 1984), abstraction or executive functioning deficits (Beatty et al., 1995; Beatty & Monson, 1996; Heaton et al., 1985; Minden et al., 1990; Rao et al., 1984 & 1987), and affective difficulties (namely depression) (Dalos et al., 1983; Feinstein, 1995; Joffe et al., 1987; Minden & Schiffer, 1987; Schiffer, 1987; Whitlock & Siskind, 1980). The findings are also consistent with Rao (1986), who was one of the first individuals to identify MS as a potential member of the subcortical dementia family of disorders. However, the deterioration documented in the present investigation was very mild in nature, such that impairment ratings reflected functioning ranging from average to mildly impaired. Nonetheless, although the degree of deficit is mild, the pattern of diminished scores remains consistent with the subcortical profile in that all four areas are affected to similar degrees.

Examination of the average impairment ratings across subjects for each measure (Tables 3 and 4) demonstrates that performance is relatively consistent across all measures. With respect to performance in each of the four domains of interest, correlational analysis revealed that the three areas reflecting cognition (i.e., attention, memory, executive functioning) were strongly intercorrelated. This again lends support to the fact that the subjects exhibited a specific pattern of deficits, rather than one or two isolated (and unrelated) problems.

The fact that the affect domain, although also mildly affected, was not significantly correlated with the cognitive measures is interesting. It was highlighted above in the introduction that the affective changes related to MS had three possible explanations: reaction to a debilitating illness, lesions in anatomical areas of the brain

associated with affect, and/or a genetic link between susceptibility to MS and to affective disorders (Garland & Zis, 1991). Given that all three cognitive domains were shown to be directly related to pathology, and that the affective domain was not (see below), it seems likely that in the case of these particular MS subjects, the second explanation can be ruled out. Thus, the affective changes can more likely be attributed to a reactive depression or to a genetic predisposition. The first explanation could be tested by comparing this group of patients, to another group of chronically ill subjects (who do not have MS). If the level of affect is comparable in the two groups then the depression could be reactive. However, if the level of affect in the MS patients is greater than the other chronically ill subjects, then the genetic predisposition explanation is more likely. This use of a particular control group relevant to the hypothesis under consideration was suggested by Rao (1986), and put to use in a study of affect and MS by Dalos et al. (1983). Dalos et al. (1983) found that MS patients reported more affective disturbance than spinal-cord injured controls.

A more detailed discussion of affect, and the potential reasons for the lack of significant relationship to pathology, can be found below.

The present study was able to assess the stability of the subcortical profile across time; something that other studies have neglected to examine. Although no significant change was found over time (see below) with respect to the *degree* of impairment as expected, the *pattern* of impairment remained consistent at both baseline and follow-up. Specifically, the four functional domains of the subcortical dementia profile were diminished throughout the duration of the study, attesting to the stability of the profile

over time.

There are a number of potential reasons why the subjects in this study were only mildly impaired in the areas assessed. First, these patients were in the very early stages of the disease process. Disease duration (from diagnosis) ranged from a few months prior to the beginning of the study, to 8 years, with a mean of 3 years. Given that MS relapses (an indicator of clinical progression of the disease) often occur with large gaps of time (e.g., sometimes in the magnitude of years) between them, the disease has not likely progressed very far in any of these individuals. Indeed, the largest number of active lesions, present at baseline or follow-up, for any given subject was 9; with the mean number being 1.38 per subject. This attests to the minimal degree of actual pathology present in these individuals.

Second, the mild nature of the impairment could be reflective of the highly educated sample. The mean number of years of education for this sample was 14. This is well above the mean for the population at large. In their 1991 census, Statistics Canada reported that 57% of the population were not educated beyond high school (14% of the population did not reach grade 9). Kaufman (1990) reported that mean IQ values differed by nearly 33 points when comparing college graduates (16+ years of education) with those attaining only elementary school levels (0-7 years education). So too, can we expect neuropsychological performance to be higher (even though diminished from premorbid levels) in a more highly educated sample (Lezak, 1983). In order to confirm this hypothesis, the neuropsychological performance of subjects in this study would have to be compared to subjects with lower educational attainment (and matched disease

duration).

Third, the mild degree of the deficits could be related to the fact that the current sample were recruited as volunteers. As is always the case in research utilizing volunteers, the subject sample may not necessarily be reflective of the general population of MS patients. Only a specific strata of the MS population at large are expected to volunteer for such a time intensive study as this. They must be highly motivated, and at the same time, their degree of disability would have to be minimal in order to facilitate their participation. For instance, if they were unable to function to near normal levels from a motoric point of view, the probability of them wanting to attempt regular trips to the hospital would be reduced.

From a theoretical perspective, these findings provide support to the notion that MS can be considered as representative of those diseases which present with neurocognitive deficits in areas subsumed under the designation "subcortical dementia." As such, cognitive and behavioural comparisons to diseases such as Parkinson's disease and Huntington's disease are appropriate, as are contrasts to "cortical dementias" such as Alzheimer's disease. This is not to say that MS cannot also be grouped with other disorders primarily affecting the cerebral white matter, such as those which, to some extent, may lead to the presentation of characteristics of the Nonverbal Learning Disabilities syndrome (White & Kregel, 1995). Indeed, Feinstein (1995) points out that MS differs from Parkinson's and Huntington's because it is predominantly a white matter disease. Given that differences in profile *within* the subcortical distinction have been made (Caine et al., 1986), perhaps white matter diseases themselves form a distinct

subset. Nonetheless, this research provides support for one conceptual framework from which MS can be viewed.

MRI Correlates of Clinical Disability

Hypothesis 2 stated that active lesion load would be positively correlated with the degree of disability as documented on the Expanded Disability Status Scale (EDSS) at both baseline and follow-up. Correlational analyses revealed that this was not the case. Nor was disability significantly related to total lesion load. Certainly, there is precedent in the literature for the lack of significant findings. Other authors have noted that pathology did not seem to be related to clinical disability to a significant degree (Jacobs et al., 1986; Reese et al., 1986), and when a significant relationship was found, it was modest at best (Filippi et al., 1995; Frank et al., 1994; Stevens et al., 1986). This is why the notion of “clinically silent” lesions was put forth. If lesions could not predict clinical disability, then they were considered as noncontributory with respect to the clinical relapses observed. Results discussed below will address the concept of “clinically silent lesions.” Clearly, the methodological improvements in this study (i.e., homogeneous subject sample, improved MRI technology, shorter interval between MRI and clinical exam), were not sufficient to improve the relationship between pathology and clinical disability.

One reason for the lack of findings in the present study is the EDSS measurement itself. The reliability of the EDSS has been called into question. Even experienced neurologists often differ in their ratings (Filippi et al., 1995). A second reason proposed by Filippi et al. (1995) may also apply to the present study. Given that some patients

received treatment with corticosteroids to treat clinical exacerbations of symptoms during the duration of the study, it is possible that this immunosuppressive pharmacotherapy could have had different effects on clinical disability as compared to pathological activity. A third potential reason is that the MRI variables took into account only brain lesions (not spinal cord lesions). Given that many of the symptoms of clinical disability detected by the EDSS could be caused by lesions to the spinal cord, the lack of significant findings is not surprising. Future studies could image the entire central nervous system. However, the cost of such a substantial amount of imaging might prove prohibitive.

In order to determine if the lack of significant findings was due to the fact that the EDSS is a summary score of various types of disability (thereby potentially overlooking correlations with a specific kind of disability), analyses were repeated substituting EDSS subscale scores. The only subscale to approach significance was the one assessing cerebral (or mental) functions. Given that these types of functions are subserved by the brain only (not the spinal cord), this finding makes intuitive sense. The lack of significance may be a function of the small sample size in the present study, or it may reflect the relative insensitivity of the measure. For instance, more sensitive measures of cognitive functioning, such as those used in a neuropsychological assessment would be more likely to yield significant results. This was indeed the case, and it will be discussed below.

A secondary finding of the above analyses was that disability was positively correlated with age at baseline, such that with increasing age, corresponding increases in disability were observed. The lack of significant relationship between disability and

disease duration rules out the interpretation that older individuals simply have had the disease for longer and thus, have more advanced degrees of impairment.

This relationship between age and disability was inconsistent, in that it was not observed again at follow-up. This suggests that the finding at baseline may simply have been an artifact of the data. Perhaps the same finding would not have been found had a larger sample size been available.

MRI Correlates of Cognitive Functioning

Preliminary correlational analyses of the attentional measures revealed significant intercorrelations between most of the tests administered. However, there were a few measures that did not correlate with the others, and thus, were excluded from the analyses. These included: Trail Making Test Part A, Digit Span forward, Visual Span, and the Gordon Diagnostic System (GDS) Distractibility subtests. Speculation regarding the reason why these particular measures were not related to the others is warranted. The fact that Digit Span forward and Digit Span backward demonstrated different patterns of correlation provides support to the notion that these two subtests should be analysed separately, as suggested by (Fischer, 1988). The degree of complexity, or difficulty level, of the first three measures (i.e., Trails A, Digit Span forward, Visual Span) is minimal. Indeed, even if one were to have significant organic involvement, it is possible to perform within normal limits on these measures. The mild nature of the deficits exhibited by the individuals in this sample may explain why they showed mild decrements on other measures but no significant problems with these. However, the GDS Distractibility subtests are more difficult tasks (i.e., continuous performance task in the face of

interference), and one would expect poorer performance on these measures. A possible explanation why this was not so, was that the Vigilance subtests were administered first. Given that the task is the same as the distractibility task (without the interference) the subjects may have been given sufficient practice, so as to improve their performance over time such that the latter task lacked the errors of the first task.

Nonetheless, the measures that were included in the attention domain tapped the following abilities: verbal tracking of information in the face of interference, mental control, simple sustained attention, sustained attention in the face of interference, and reaction time (or speed of processing). The mild degree of impairment on these measures is consistent with the results documented in the literature regarding performance of MS patients on tasks of attention and information processing speed (Beatty et al., 1988; Feinstein et al., 1993; Heaton et al., 1985; Kujala et al., 1994 & 1995; Litvan et al., 1988; Rao et al., 1989; White & Krenzel, 1995).

Hypothesis 3 proposed that active lesion load would be positively correlated with deficits in subcortical neuropsychological functioning at both baseline and follow-up. Each functional domain will be addressed in turn.

Correlational analyses revealed that the attention variable was not significantly correlated with active lesion load at baseline or follow-up as hypothesized. However, a significant correlation was obtained with total lesion load (burden of disease) for both occasions. Thus, although attention was not significantly related to *current* disease activity, as measured by gadolinium-enhanced T1-weighted imaging, it was related to *overall* disease activity, as measured by T2-weighted imaging. Although active lesions

are better detected on enhanced scans, T2-weighted imaging can detect some of the reactivated old lesions and larger active lesions.

The relationship between the T2-weighted MRI variable and cognition that is exhibited here has also been reported by several other authors (Anzola et al., 1990; Franklin et al., 1988; Huber et al., 1987; Izquierdo et al., 1991; Medaer et al., 1987; Rao et al., 1989; Ron et al., 1991; Ryan et al., 1996). However, the methodological improvements in the current study appear to have had an impact on the findings, in that the magnitude of the relationship exhibited here is stronger than others have reported. The mean Pearson correlation coefficient (for both baseline and follow-up) between attention and total lesion load was $r = .62$. A comparable mean value from Franklin et al. (1988) was $r = .35$. According to Cohen (1988) the latter value is reflective of a medium effect size. The value from the present study represents a very large effect size (especially when one considers the small sample size).

Methodological improvements in the present study are likely contributors to this stronger relationship. The magnitude of the field strength of the MRI machine used in the present study was larger than that used by Franklin et al. (1988) (i.e., 1.5T as opposed to 0.15T respectively), according to recommendations for clinical trials proposed by Miller et al. (1991). Thus, more lesions were likely detected. Using the same field strength as the present study, Huber et al. (1992) also found a larger mean effect size ($r = .51$). Improvements in method in the present study also included the smaller time interval between MRI and cognitive testing, and a more homogeneous subject sample (only relapsing-remitting patients).

Thus, the direct relationship between pathology (as detected by MRI) and neurocognitive functioning, as documented in the past, has been re-established. These findings argue against the interpretation that lesions not related to clinical disability (as assessed in a standard neurological exam) are clinically-silent. Although disease activity can go undetected in such an examination, the present findings provide support to the notion that lesions may lead to subtle cognitive deficits that are only detected by a more detailed neuropsychological assessment. Thus, the theoretical utility of a concept such as “clinically-silent” lesions comes into question. Perhaps, rather than assuming that the lesions have no direct impact on functioning, we should assume that we simply need to use, on a more routine basis, assessment techniques with a greater sensitivity to the subtleties of disease progression.

There are a number of reasons why active lesion load did not correlate significantly with cognition. First and foremost, is the nature of the measurement itself. The active lesion load was calculated by simply adding the number of newly enhancing lesions to the number of persistently enhancing lesions. The size, or surface area, of these lesions was not recorded. Thus, two individuals, both with one active lesion, could actually have significantly different amounts of disease burden, depending upon the size of the lesions. For example, at baseline in the current study, subject #1 had one active lesion with 4546.1 mm² of surface area. Subject #13 also had one active lesion, but with only 267.6 mm² of surface area. Clearly, the active lesion load measurement does not reflect the actual amount of pathological activity. This is a significant limitation of this type of measurement. But, although the surface area of active lesions would be more

helpful, it is much more difficult to obtain an accurate estimate of this because of the nature of disease activity. As outlined in the introduction, active lesions are surrounded by an area of inflammation (Powell and Lampert, 1983). It is often difficult to determine on an image, how much of the highlighted area is actual disease activity, and how much is simply inflammatory activity. As such, an accurate surface area measurement of active lesion load would be difficult to obtain.

A second potential reason for the lack of relationship between active lesion load and cognition is that it does not represent the totality of brain damage. Indeed, although active lesions likely contribute to some of the cognitive impairment, so too, do old lesions. Just because old lesions are no longer cellularly active, does not mean that the tissue then becomes functional again. Damage is damage, no matter if it is old or new. Thus, cognitive processes that rely upon the gray matter that is damaged, or the white matter that carries information to and from various areas of gray matter, are no doubt compromised. If localization data were available, it is possible that specific active lesions could be correlated to specific cognitive processes, but they are unlikely to be related to cognitive deterioration as a whole.

A third potential reason for the lack of correlation with active lesion load is the very nature of the pathological changes themselves. During the demyelination process, the neurons themselves are spared until the later stages of the disease (Mattioli et al., 1993). It is possible then, that the older lesions detected on T2 had progressed to the point that the neurons themselves were destroyed; thus, contributing to cognitive deterioration. Newer lesions detected with gadolinium may not have had sufficient time

to destroy the neuron itself, allowing for some sparing of functioning (albeit not as efficient as if the myelin was present).

A number of control variables were included in the analyses. The only two yielding significant correlations with cognitive variables were education (at follow-up only) and disease duration (baseline and follow-up). In addition, these variables did not correlate significantly with any of the other cognitive variables. Traditionally, if education were to have an effect on neuropsychological performance, individuals with lower education would perform worse than those with more education (Prigatano & Parsons, 1976). The opposite pattern was observed here. In the present study, education was positively correlated with degree of cognitive impairment, so that as education level increased, so did the degree of attentional impairment. This is counterintuitive, and is likely an artifact of the data; especially when one considers that this variable was significant at follow-up only. Our sample was more highly educated, on average, than the general population. All subjects had completed high school, with 58% completing some form of post-secondary education. In addition, in this sample, the distribution of subjects with respect to their education does not reflect the normal distribution of the population at large. In order to confirm this explanation, the study would have to be repeated with a larger number of subjects with a greater range of educational attainment. The present study was unable to achieve this, perhaps as a result of the nature of the study itself (i.e., a lengthy battery of cognitive tasks). This may have precluded less educated individuals from participating simply because it would have been intimidating to participate in a research study that itself may have been perceived as an academic-type

task.

The second control variable that correlated with the attention variable was disease duration. In the literature, findings vary with respect to the role played by disease duration in studies similar to this one. Some authors have found that disease duration significantly impacts neuropsychological performance (Ron et al., 1991; Stevens et al., 1986), whereas others have found no such relationship (Feinstein et al., 1992; Frank et al., 1994; Rao et al., 1985 & 1989; Reese et al., 1986). These findings seem to suggest that in some MS patients, the relationship between number of years of disease and actual disability (or cognitive deterioration) follows a linear course. Specifically, as the duration of disease increases, so too, does the amount of dysfunction. However, in other individuals with MS, the relationship is not so straightforward; perhaps following a pattern that is more difficult to quantify.

In the present study, the significance of the relationship between disease duration and attention suggests the more linear relationship. However, the fact that disease duration did not correlate significantly with either of the other two cognitive variables (memory and executive functioning) implies that this explanation is not sufficient. It is possible that it is the unreliability of this measurement that contributes to the lack of consistent findings across cognitive domains. The disease duration measurement is actually an estimation. Not only can it vary considerably depending on whether one considers time zero as the onset of symptoms, or the date of the diagnosis; but further variability is contributed by other factors (i.e., when subject first notices symptoms and how severe those symptoms are, when the patient presents to the physician, availability of

a physician experienced at MS diagnosis, bias in interpreting diagnostic criteria, and waiting periods for confirmatory tests [e.g.,MRI, lumbar puncture]). Rao (1986) stressed that the diagnosis of MS is often difficult to make in the early stages of the illness, thus, a patient could exhibit the disease but not be diagnosed until sometime later. It is these reasons that have likely contributed to the inconsistent impact of disease duration on cognitive functioning, as assessed in the present study.

After the correlational analyses were completed, the significant variables were entered into a multiple regression analysis in order to determine what percentage of the variability in attention could be attributed to those variables. The order of entry into the regression equation was determined by the examiner. According to statistical tradition, control variables should be entered before the variable of interest, so that the regression analysis can essentially serve as an analysis of covariance. The significance of lesion load can be assessed after partialling out other nuisance variables. This rationale was followed for these analyses, resulting in the fact that total lesion load did not contribute any additional variance to attention beyond that afforded by education and disease duration.

But, given the problems with the control variables (i.e., education and disease duration) mentioned above, the analysis is not particularly meaningful. If the contribution of education is simply a spurious finding (data artifact) and if disease duration is an unreliable measurement, then the findings hold no theoretical importance. As such, the multiple regression analyses were re-done with a different ordering of variables into the regression equation. In their comprehensive textbook on multivariate

statistics, Tabachnick and Fidell (1996) state that “variables with greater theoretical importance could also be given early entry” into the regression equation. So, in order to increase the theoretical implications of the findings, total lesion load was entered first, followed by education and disease duration. Results revealed that at baseline and follow-up, 35% (28% adjusted) and 41% (35% adjusted) respectively, of the variance in attention was predicted by total lesion load, and that education and disease duration did not provide any further significant variance.

These latter analyses are more meaningful from a theoretical perspective. The findings suggest that the severity of attention impairment in any given patient with MS can be predicted by the degree of pathological activity as documented on MRI. Once again, this lends credence to the notion that few lesions can be considered clinically silent if cognition is so clearly related to pathology.

It should be noted that given the number of variables entered into these multiple regression analyses (2 at baseline, 3 at follow-up), the number of subjects should have been higher if strict statistical guidelines were applied. Given that this study is exploratory in nature, and the fact that the correlational analyses yielded such large effect sizes, the analyses were considered justified. However, caution should be taken when attempting to generalize the findings to relapsing-remitting MS patients as a whole. Ideally, the study should be repeated with a larger subject sample. The discussion of the power analyses below will address this point.

With respect to the memory domain, preliminary correlational analyses demonstrated that several subtests of the California Verbal Learning Test and the Rey

Visual Design Learning Test were significantly correlated. The one aspect of memory that did not appear to be correlated with the others was verbal recognition. Verbal recognition appeared to remain relatively intact, whereas other aspects of memory were diminished to a similar degree. The findings on the verbal recognition task suggest that verbal encoding of information was preserved in this sample. This would certainly be consistent with the subcortical dementia profile which suggests that recall shows more deterioration than encoding. However, the fact that visual encoding (as measured by the RVDLT recognition trial) was diminished runs contrary to this explanation. As reviewed in the introduction, the literature is also inconsistent with respect to the preservation of encoding in MS. Perhaps, as White and Krenzel (1995) suggest, the problems stem from *inefficient* encoding and slowed information processing (the latter is evident in this sample), and that with repeated exposure proper encoding, or learning, of information would be possible. Clearly then, there is a need for a future study to address this issue specifically. Which is more often diminished in individuals with MS, encoding or retrieval; and if encoding is affected, can it be enhanced with continued exposure?

As was discussed above in reference to attention, active lesion load was not correlated with memory performance. Nor were any of the control variables (for reasons addressed above). Once again, total lesion load was the pathological variable that was related to memory dysfunction. Specifically, total lesion load accurately predicted 38% (31% adjusted) of the variability in the memory variable. However, in contrast to the findings for attention, memory was predicted by total lesion load at baseline only. At follow-up, performance on the memory measures was not correlated with any of the

control variables, nor was it related to the degree of overall pathology.

One of the hallmarks of relapsing-remitting MS is the fact that clinical symptoms wax and wane. So too, can the pathology itself wax and wane. Specifically, inflammation occurs following blood-brain barrier breakdown and then subsides as the active lesion phase is over (Powell & Lampert, 1983). In addition, some attempts are made at remyelination, although the myelin produced is abnormal (Powell & Lampert, 1983). Although not significant, there was a trend for memory performance to be slightly better at follow-up as compared to baseline. It is possible that corresponding changes in pathology also occurred. Given the relationship between memory functioning and pathology at baseline, perhaps the detected lesions were present (at least in part) in the temporal lobes, an area of the brain commonly thought to subserve memory functions. By the time of follow-up it is possible that the pathology (although remaining constant with respect to overall surface area) was no longer as apparent in the temporal lobes. Attention may be less vulnerable to changes in lesion site given that these types of tasks tend to encompass many different aspects of brain functioning (i.e., attention is susceptible to degradations in functioning when any organic damage is present regardless of specific location). Future studies which are able to include localization data would be able to clarify this point.

A second potential reason for the lack of correlation may simply have been an artifact of statistical properties of the two variables. Although neither memory or total lesion load changed significantly over time, there was a trend for the degree of memory impairment to decrease and the degree of pathology to increase. These subtle changes.

although not of sufficient magnitude to account for statistical changes *within* the variables, may have been of sufficient magnitude to affect the relationship *between* the two variables. Especially when considering that their numeric trends are in opposite directions.

With respect to the executive domain, preliminary correlational analyses revealed that some aspects of the Category Test and the Wisconsin Card Sorting Test (WCST) were correlated. The two measures were administered at baseline and follow-up, respectively, in order to avoid the practice effects that are inherent to these two measures. The total number of errors on the Category test was correlated with the number of perseverative responses and errors on the WCST. This makes intuitive sense given that perseverative responding on the Category test would contribute to a higher error score. The reason that Category errors did not correlate with the number of sorting categories achieved on the WCST is less clear. Perhaps it is because the changing of mental set that takes place with respect to the Category test is more clearly defined by the organization of the test itself. Specifically, the subject knows that with the beginning of each new subtest, they may have to change their way of thinking in order to obtain the correct answer. With the WCST, the changes in mental set are not so clearly defined by the structure of the task. There are no subtests. The subject learns only that their mental set no longer applies by the negative verbal feedback provided by the examiner. It usually requires the commission of at least a few errors before the subject realizes that the rules have changed. Thus, in one sense, the WCST is a more difficult task since the changes in set are not inherent to the structure of the task. As a result, the two tests yield different

patterns of responding in this regard.

The two other measures that contributed to the executive domain score were the Trail Making Test Part B and the Modified Stroop mental shifting task. Both of these tasks have a mental shifting component that is somewhat different from the two tests discussed above. Rather than making a mental shift and then staying with that mental set until the next shift, these two tasks require a constant shifting back and forth between two mental sets. For Trails B the subject must switch from number to letter, and for the Modified Stroop the subject must first read the word and then name the colour of ink. In addition to this constant shifting, or divided attention, the two tasks also require sustained attention.

One shortcoming with the use of the Trail Making Test is the motoric demands of the task. Rao (1986) recommends the use of cognitive measures which do not rely on intact motor functioning, given the physical disability often concomitant with MS. Ideally, if the Trail Making Test were to be used, one should subtract the Trails A time score from the Trails B time score in order to factor out the motoric component and leave only the time required for mental shifting. This would have been done in the present study were it not for the fact that in order to calculate the Average Impairment Ratings (AIRs), sufficient normative data from the contributing measures was required. Given that no proper normative data has been established for the B minus A findings, this method could not be used in the present study. However, given the low physical disability scores in this sample (EDSS less than or equal to 4.0, with a mean value of 1.96), slowed motoric functioning did not likely confound results significantly. This is

given more credence when one considers that the degree of impairment documented on the Trails B task was consistent with the degree of impairment on other executive tasks that did not require a motoric response.

As with the other cognitive domains, active lesion load did not correlate with decrements in executive functioning. Nor did the control variables (see above for potential explanation). However, once again, total lesion load did prove to be significantly related to executive ability. Specifically, total lesion load accounted for 44% (39% adjusted) and 49% (44% adjusted) of the variance in executive functioning, at baseline and follow-up respectively. These findings suggest that the degree of overall pathology is sufficient to predict the degree of executive dysfunction in this group of relapsing-remitting MS patients. The consistency of this relationship across the 6-month time span of the study attests to the stability of this particular aspect of cognitive dysfunction despite potential changes in the locale of lesions. Future studies may wish to use localization data to predict whether or not executive deficits are better predicted by overall brain lesion area or by lesions in specific brain regions (e.g., frontal lobes?).

MRI Correlates of Affect

The three measures of affect that were employed in the current study demonstrated significant intercorrelations with each other, so as to warrant their inclusion in the primary correlational analyses. Four aspects of emotional functioning were assessed: depression, hopelessness (or despair), and both state and trait anxiety. Each measure contributed to the calculation of the average impairment rating for affective disturbance as a whole.

When assessing the relationship of affect to the control variables, a significant negative correlation was found between education and affect at baseline. Specifically, as education level increased, affective disturbance decreased. When attempting to determine why this was so, it was speculated that perhaps individuals with higher education were working in jobs that did not require as much physical activity as those with lower education. As such, the jobs of the more highly educated individuals may not have been impacted as much by the disability inherent to their disease; resulting in fewer insults to their self-esteem.

In order to determine if occupational status did indeed impact on affect, two analyses of variance were performed to determine if subjects in specific employment groups (i.e., Analysis 1 = employed versus unemployed; Analysis 2 = those on disability, unemployed, white collar, and blue collar) differed with respect to affect. The findings were not significant. Therefore, the impact of education on affect did not appear to be related to the occupational attainment often concomitant with educational differences.

Given that education was related to affect at baseline only, the poor stability of this relationship over time was established. This brings into question the significance of the finding. Perhaps it is simply a spurious finding, and is an artifact of problems with the data. As discussed above, the educational attainment of our sample was not representative of the general population, nor were our subjects normally distributed with respect to education. This explanation does appear to be the most likely.

In contrast to the three cognitive aspects of the subcortical dementia profile (i.e., attention, memory, executive functioning), affect did not correlate significantly with total

lesion load. Nor did it correlate significantly with active lesion load. One potential confounding variable was that some subjects received treatment with corticosteroids throughout the study in order to treat clinical exacerbations. The literature indicates that this type of pharmaceutical treatment has been implicated as a potential cause of depressive symptoms (Garland & Zis, 1991; Whitlock & Siskind, 1980).

Nonetheless, the lack of relationship with pathology suggests that in this sample of patients there is likely little involvement of brain structures that have been known to be implicated in emotional functioning (e.g., limbic system). As noted above, Garland and Zis (1991) suggested that the affective difficulties concomitant with MS could have three potential explanations, of which pathological causes was only one. As stated above, these data suggest that the other two explanations are more likely in this particular sample of individuals: affective disturbance may be a reaction to a debilitating illness and/or the presence of MS may imply a genetic predisposition to affective difficulties. In order to confirm the lack of limbic system involvement, the study would have to be replicated using MRI localization data.

If the affective changes are reactive in nature, then affect may be mediated, in part, by situational or environmental variables. Specifically, whether or not one feels supported by those around them may have been contributory. Certainly, social support has been shown to contribute to lessened vulnerability to stress (Zimbardo, 1985). Feinstein et al. (1992) reported that perceived social stress and support did contribute to depression ratings in their sample. As such, correlational analyses were conducted to determine if perceived social support from various sources (i.e., parents and relatives,

children, friends, religious organizations, secular organizations, health care professionals, and any other source indicated by the subject) contributed to the degree of affective disturbance. No such relationship was found. Thus, if the affective difficulties exhibited by these subjects was reactive in nature, it was not influenced by whether or not they perceived their environment as supportive. However, it should be noted that perceived social support was not measured psychometrically. Perhaps different results would have been obtained if a more formal measure of social support were utilized. Nonetheless, the results seem to bring into question the possible reactive nature of the depression, and suggests that a genetic predisposition may seem more likely. Further study is required.

Affective disturbance at follow-up was related to the number of clinical exacerbations that occurred between baseline and follow-up. As the number of exacerbations increased, so too did affective disturbance. Thus, although the number of exacerbations did not correlate significantly with pathology or cognitive variables, it did have an impact on the subjects' emotional functioning. This is consistent with the findings of Dalos et al. (1983), who found a significant positive relationship between clinical exacerbations and psychiatric morbidity.

From a review of the literature in this area, Feinstein (1995) found that there have been several examples of the association between the pathology of MS and cognitive dysfunction, but researchers have not as yet documented a similar relationship with respect to affective disturbance and pathology. He also elucidated several methodological difficulties that have plagued this research and have contributed to the lack of significant findings. The one methodological flaw he described that appears to be

the most relevant to the current study, is that self-report measures are inadequate to assess depression. Thus, although the MRI technology in the present study appears adequate, the lack of depression ratings derived from a structured clinical interview (e.g., DSM-IV-based), probably contributed to the lack of significant results. Other methodological difficulties in the current study include the small sample size, and the lack of localization data. Consistent with Garland and Zis (1991), Feinstein (1995) concluded that the etiology of depression in MS is likely multifactorial. Thus, although pathology may contribute to the expression of depressed affect, it is not the only contributing factor.

Disease Progression

Hypothesis 4 predicted that the change in total lesion load would be correlated with the change in subcortical neuropsychological variables overtime (i.e., between baseline and 6-month follow-up). This was not the case. Further, most variables showed no progression over time. Specifically, no changes were documented with respect to demyelination (i.e., pathology as detected by MRI), attention, memory, or affective disturbance. The only variable to exhibit some degree of change was executive functioning. Less impairment was noted at follow-up when compared to baseline. This finding should be interpreted with caution given the fact that different measures were administered on the two occasions. Although the Category Test (baseline) and the Wisconsin Card Sorting Test (WCST; follow-up) were correlated to a significant degree, they are not equivalent. As such, any variability between the two measures may have contributed to the difference observed over time with respect to executive functioning. Although practice effects on the two executive measures that were administered on both

occasions (i.e., Trail Making Test Part B, Modified Stroop mental shifting) are possible, this explanation is unlikely. The nature of the tasks do not lend themselves to practice effects over such an extended period of time.

It is also possible that the improvement in executive functioning simply represents a regression back toward the mean. Kerlinger (1986) discusses this *regression effect*. Test scores change over time due to purely statistical reasons, and on retest, more often than not, they will move closer to the mean value for that particular test. Kerlinger (1986) stated that “on the pretest some high scores are higher than “they should be” due to chance, and similarly with some low scores. On the posttest it is unlikely that the high scores will be maintained, because the factors that made them high were chance factors - which are uncorrelated on the pretest and posttest. Thus the high scorer will tend to drop on the posttest” (p. 297). The opposite pattern can be observed for the low scorer. Given that the standard deviation of the executive average impairment rating variable was larger at baseline ($SD = .824$) than at follow-up ($SD = .507$), meaning that there were more extreme scores on the first testing occasion, this explanation seems plausible. Thus, the improvement in executive abilities could have been purely statistical in nature rather than reflective of a true improvement in cognitive functioning.

The alternative explanation is that executive functioning actually did improve over time. Once again, localization data would prove useful here, as the change (if significant) was most likely related to pathological changes. Perhaps, more disease activity and inflammation was evident in the frontal lobes at baseline.

The lack of relationship between the change in pathology and the change in the

cognitive and affect variables is due, in part, to the fact that no substantial change took place in each variable. The lack of relationship also suggests that the methodological improvements in the current study (i.e., shorter interval between MRI and neuropsychological testing, consistent follow-up interval, randomized test presentation) were not sufficient, in and of themselves, to improve the relationship.

The primary reason for the lack of change over time is likely that the time interval between baseline and follow-up was not sufficient. Indeed, in a sample of relapsing-remitting patients at such an early stage in their disease as these subjects are, MS often does not progress at a very rapid rate. The time interval between clinical exacerbations can often be months or years. Thus, although the 6-month time interval was of sufficient length to meet the guidelines for clinical trials proposed by Miller et al. (1991), it was not long enough to track the disease progression in these particular subjects. Ideally, a longitudinal study should be performed over several years in order to properly monitor both the progression of demyelination, as well as the corresponding deterioration in cognitive and affective functioning. Given that Mariani et al. (1991) followed their patients for 2 years and still did not find any significant change over time, the duration should be even greater than 2 years. However, with such a lengthy period of time, the likelihood of subject attrition is increased significantly. Subjects may rapidly lose interest in a study which requires such a significant time commitment on their part. As such, large subject numbers would be required to counteract the attrition. Given the significant cost of MRI studies, this criteria may prove prohibitive.

Instrument Reliability

Given the lack of significant change in attention, memory and affect, and the questionable change in executive functions, over time, the stability of the actual measurements over the two test occasions was considered. Specifically, test-retest reliability coefficients were calculated. First, for the overall domain scores, and second, for the individual tests themselves.

Anastasi (1988) suggests that it is desirable for reliability coefficients to be in the magnitude of .80 or higher. The reliability coefficients for all three cognitive domains were able to meet this criteria (attention = .80; memory = .89; executive = .88). The high coefficient for the executive measures also provides support to the notion that the improvement in executive functioning, reported above, was likely due to a regression toward the mean rather than actual cognitive improvement.

If one examines the reliability coefficients for each of the measures which contributed to those overall domain scores, one is able to see that not all measures demonstrated significant reliability. For instance, in the attention domain, only 5 of 12 measures exhibited reliability coefficients of the magnitude recommended by Anastasi (1988). The most reliable measures were as follows: Consonant Trigrams 9 second delay, Digit Span backwards, Modified Stroop Color time, Stroop Color score, and Stroop Word score. It is interesting to note that each of these values represents only a particular aspect of the tests. For instance, although Stroop Word score and Color score were reliable measures, the Stroop Word/Color score was not. Also of interest is the fact that none of the scores from the Gordon Diagnostic System (a continuous performance

test) were reliable. Thus, reaction time may have been more sensitive to the changes in functioning over time than the other attention measures.

In the memory domain, 6 of 9 measures were of large enough magnitude to be considered reliable: CVLT Long Delay Cued and Free Recall, CVLT Short Delay Cued and Free Recall, RVDLT Trial 5, and RVDLT Total correct. Given that alternate forms were administered for both of these measures, these values represent alternate-form reliability rather than test-retest reliability. Both of the executive measures that were administered on both occasions were reliable: Modified Stroop Mental Shifting, and Trail Making Part B.

The error variance of the reliable measures, and the fact that not all measures demonstrated reliability, can be explained by chance fluctuations. These fluctuations may be environmental in nature, or they may be related to subject variables (Anastasi, 1988). For instance, subjects' scores may have changed because of environmental variables such as a distracting noise outside of the testing room or the presence of a different examiner. More likely, in this sample of subjects, the fluctuations with respect to the subjects themselves were more contributory. For instance, they may have been fatigued on one testing occasion, or have been distracted by a physical symptom of the MS. The changes resulting from pathology (although shown to be statistically nonsignificant) likely accounted for some variations.

The test-retest reliability of the affect domain, as well as the individual tests within that domain, exhibited a different pattern than the cognitive measures. Specifically, absolutely no correlation was found between the affective domain at

baseline and the same value at follow-up. However, the t-test revealed that no significant change was observed over time with respect to this variable. This suggests that the mean level of affective disturbance remained constant across the two testing occasions, but that a different pattern of subject responding occurred. For example, someone that had few affective symptoms at baseline, would demonstrate more affective disturbance at follow-up. The opposite pattern would be true for those with more affective symptoms at baseline. Given this variability within the subject sample over time, it would appear that the measures employed tapped situational affective disturbance rather than more stable characterological personality traits. This lends support to the notion that, at least some of the depression exhibited by these subjects, may be reactive in nature. If not to the disease itself, perhaps to the implications the disease has on their daily functioning, or to other stressors that are present in their lives. The supposition that one half of the State-Trait Anxiety Inventory measures trait, or characterological, anxiety, comes into question given the lack of consistent findings on this measure over time.

None of the four affect measures demonstrated a significant degree of test-retest reliability, according to the acceptable values suggested by Anastasi (1988).

One consideration that should be stressed is the fact that test-retest reliability always decreases with an increasing time interval between test occasions (Anastasi, 1988). This may account, in part, for the smaller reliability coefficients. Given that most test-retest reliability coefficients reported in reference to specific tests are over a much shorter interval (i.e., a few weeks), it would be unwise to compare the present findings with published normative data. Especially when one considers that “the concept of

reliability is generally restricted to short-range, random changes that characterize the test performance itself rather than the entire behavior domain that is being tested” (Anastasi, 1988, p. 118).

Statistical Power

According to Cohen (1988) small, medium, and large effect sizes will yield Pearson coefficients of $r = .10$, $.30$, and $.50$ respectively. All values yielded in the primary correlational analyses of this study (i.e., regarding the relationship between MRI pathology and neuropsychological variables) were well above $.50$, suggesting that the effect sizes were very large. This attests to the strength of the relationship between the variables under consideration. However, given the small sample size, calculated power values are less than ideal. Most researchers strive for statistical power of $.90$ or greater in order to be confident that the results they are reporting are indeed correct. The power values reported here for the relationship between predictor variables and neuropsychological variables were low enough to warrant caution in interpreting results. For future research, simply doubling the sample size to 24 would enhance power to over $.90$ if the strength of the relationships remained constant. Although this would likely require the participation of more than one centre (i.e., hospital or MS Clinic), the recruitment of 24 subjects for such a study is feasible.

The largest power value calculated here was for disease duration. This suggests that the significant correlation between disease duration and the attention AIR has a greater chance of actually being correct than do the correlations with the other variables (TLL and education). The probability that disease duration does, in actual fact, correlate

significantly with the attention AIR is 74%. Equivalent values for TLL and education with the outcome measures are 66% and 64%, respectively. However, one consideration that is not reflected in the power calculation is the questionable reliability of the disease duration measurement itself. In order to circumvent this problem, future studies should ideally enlist two experienced neurologists (with knowledge of MS diagnosis) to calculate disease duration. Inter-rater reliability coefficients could then be calculated. If ratings of duration were significantly related then the likelihood that power is actually .74 would be greater.

CHAPTER 9

STRENGTHS AND LIMITATIONS

Although many methodological improvements have been incorporated into this study, there remain a number of weaknesses that should be pointed out. As with any study, awareness of the limitations may aid researchers in the design of future studies.

First, one must consider that the *mild* degree of impairment exhibited on neuropsychological measures may be an exaggeration of actual cognitive symptomatology, given that these patients come from a clinical (hospital-based) volunteer sample rather than from a community-based sample. As such, the sampling criteria itself may have biased the results to reflect a greater degree of impairment than is actually present in the MS population as a whole. Use of a community-based sample has been recommended by Rao (1986).

The current study failed to contrast performance on measures of “subcortical” functioning, with performance on measures of “cortical” functioning. Thus, although it has been concluded that subjects do indeed exhibit aspects of the subcortical profile, it cannot be inferred that these deficits are to the exclusion of other “cortically-based” deficits (e.g., aphasia, acalculia, etc...).

With respect to the generalizability of the current findings. Given that the sample was drawn from a population of individuals with relapsing-remitting MS, the results cannot be generalized to other MS populations (e.g., chronic progressive). However, given that chronic progressive patients are generally more cognitively impaired than relapsing-remitting patients (Heaton et al., 1985; Rao et al., 1987), one can speculate that

the degree of impairment exhibited here would be amplified in individuals with the chronic-progressive form of the disease.

The small sample size utilized in this study is also a limitation. However, the very nature of the study prohibits greater numbers given the significant financial resources required, and the time commitment necessary. Nonetheless, the statistical power of the findings is reduced, and caution must be exercised with respect to generalizing the conclusions to other individuals with MS. In addition, the small sample size limited the number of analyses that could be performed, thus, necessitating the calculation of summary ratings (average impairment ratings) rather than performing the analyses on the individual test results themselves. This may have “washed out” any significant effects that may have been present for individual tests.

Other limitations include the following: the active lesion load measurement does not reflect actual surface area, no lesion localization data was available, and depression was not assessed using a structured clinical interview.

In addition to these limitations, this study also had a number of strengths that allowed this study to build upon the findings of previous investigators in this research area.

First, this study addressed all four aspects of the subcortical dementia profile described by Cummings and Benson (1984). Very few investigators have assessed all four aspects. The fact that the conclusions of this study can be examined within this framework allows for more theoretically-based conclusions. In addition, the stability of this subcortical profile over time was addressed; something that has not been specifically

addressed in the past. The fact that relatively consistent findings were documented at baseline and at follow-up, lends further support to the relevance of this particular interpretation of the findings.

The extremely homogeneous nature of the subject sample was another significant strength. Most studies in the past have relied on a heterogeneous group of patients with varying disease courses and considerable variation with respect to duration of disease and degree of disability. The fact that all subjects in this study were similar with respect to disease course, disease duration, and EDSS ratings, as well as the fact that stringent inclusion and exclusion criteria were adhered to (e.g., psychiatric history, medication use, EDSS ratings, etc.), attests to the well-controlled nature of the study.

An attempt was made to meet the guidelines for clinical trials proposed by Miller et al. (1991). This greatly increased the methodological elegance of the study. Specifically, the current study adhered to the following criteria: a sufficient MRI field strength, the use of contrast enhancement, inclusion of subjects with a relapsing-remitting course, clinical assessments conducted in conjunction with serial scanning, adequate study duration (i.e., 6 months), repeated measures design, and recording of all new, enlarging, and enhancing lesions. These methodological improvements certainly enhanced the statistical power of the findings, despite the fact that the actual power calculations do not take them into account.

CHAPTER 10

DIRECTIONS FOR FUTURE RESEARCH

Future research could take several directions; the roots of which stem from the findings of this study. First, the present study could be replicated with the addition of control groups, such as another chronic illness (e.g., spinal cord injuries), other subcortical disorders (e.g., Parkinson's disease, Huntington's disease), and other conditions which affect white matter in adults (e.g., traumatic brain injury, tolulene-induced encephalopathy). This replication would allow for a direct comparison of both the pattern of pathological changes in each group, as well as the pattern of cognitive functioning. It would also provide insight into the etiology of affective difficulties (i.e., if the chronic illness group was similarly depressed, then the depression in MS more likely contains a reactive component). Comparisons could be drawn between MS and other subcortical diseases, as well as between MS and other white matter diseases, in order to see which group of disorders exhibits the most similarities to MS.

Second, in order to provide further support regarding the presence of the subcortical dementia profile in patients with MS, measures designed to tap more "cortically-mediated" functions could be administered (e.g., tests for aphasia, apraxia, etc.). MS patients would be expected to exhibit preserved functioning on these tests. Comparisons to subjects presenting with Pick's disease or Alzheimer's disease would allow researchers to contrast performance between these groups. The lack of cortical dysfunction expected in MS subjects would provide further support to the supposition that they exhibit a subcortical dementia profile.

Third, the study should be replicated with specific focus on the localization of lesions. Hypotheses regarding specific lesions sites and specific neuropsychological consequences could be put forth. For instance, analysis of lesions in limbic structures to predict affective functioning, and lesions in the temporal lobes to predict memory functioning would be interesting to explore. The availability of localization data would also allow more direct study of the effects of active versus old lesions on specific aspects of cognitive functioning. Other changes in the measurement of pathology could include the calculation of a lesion score that would reflect the totality of disease burden (i.e., those lesions detected on T2, plus those lesions detected with gadolinium (and not by T2)). Thus, a total lesion load measurement would include both old and new (active) lesions together in one measurement.

More research is also needed around the issue of memory functioning in MS. The present findings do not allow sufficient conclusions regarding the presence of deficits in encoding versus recall, since some aspects of encoding were affected and others were not. It is still not known whether or not the encoding difficulties stem from actual learning problems, or simply inefficient encoding resulting from poor attention and insufficient exposure time to information. More in-depth analysis of memory functioning in MS is required in order to elucidate the findings.

Future studies which are able to utilize larger sample sizes should attempt to analyse results separately for each individual neuropsychological measure administered rather than use summary measures, as was done in the current study (e.g., all attention measures grouped together as one global measure of attention). This would allow

researchers to understand which particular aspects of cognition are affected. For example, the current findings suggested that reaction time measures may have been more sensitive to changes in cognition over time than other measures of attention. Thus, by analysing these measures separately in the future, more conclusions could be drawn regarding the nature of the attentional deficits.

The fact that neuropsychological variables demonstrated significant correlations with pathology when clinical disability ratings did not, is sufficient to justify the inclusion of a neuropsychological battery as a measure of outcome in future clinical trials. Although neuropsychological testing is often a component of clinical trials evaluating antipsychotic medication in psychiatric populations (e.g., schizophrenia), this type of assessment is often excluded from the follow-up of diseases representative of general medicine populations. The cognitive dysfunction inherent in MS must be recognized. Although MS is a disease which causes significant physical disability, these individuals are also plagued by cognitive deterioration that can be just as disabling as any physical manifestation of the disease.

CHAPTER 11

SUMMARY AND CONCLUSIONS

The subjects in this study who presented with early-phase relapsing-remitting MS were found to exhibit mild decrements in neuropsychological functioning in the areas of attention and information processing speed, memory, and executive functioning. Similarly, these subjects also exhibited a mild degree of affective disturbance. Both the degree, and the pattern, of deficits remained stable over the six-month time period evaluated in this study. Three explanations were provided with respect to the mild nature of the deficits: little pathology is present in the early stages of the disease, the sample was highly educated, and the sample consisted of highly motivated volunteers.

Clinical disability ratings did not correlate with active lesion load or total lesion load. The methodological improvements of the current study were insufficient to strengthen this relationship. The reasons for the lack of findings were likely threefold: the reliability of the Expanded Disability Status Scale is questionable, treatment with corticosteroid medication may have had a differential impact on disability versus pathological activity, and the spinal cord was not imaged (a part of the central nervous system which causes physical disability when lesions are present).

Neuropsychological functioning was a better indicator of disease activity than ratings of clinical disability. Total lesion load was correlated with attention at both baseline and follow-up. The methodological improvements made in the current study accounted for the higher values of the correlation coefficients when compared to the results of past studies. These findings (along with those regarding memory and executive

functioning) argue against the notion that lesions can be clinically silent.

Although the control variables education and disease duration were correlated with attention, the validity of these findings was questioned. Specifically, the education finding may have been spurious given that the subject sample was more highly educated than the normative population, and the fact that subjects were not normally distributed with respect to education. The reliability of the disease duration measurement was also called into question. Multiple regression analyses revealed that education and disease duration accounted for no further variance in attention beyond that accounted for by total lesion load.

Memory was also found to correlate significantly with total lesion load, but at baseline only. The lack of significant findings at follow-up may have been due to changes in the location of pathology, or simply due to statistical artifact. A consistent relationship between executive functioning and total lesion load was exhibited at both baseline and follow-up.

Total lesion load did not correlate significantly with affective disturbance. This finding may have resulted from the fact that some patients were treated with corticosteroid medication (which may cause depressive symptomatology), and the fact that affect was not measured by a standard clinical interview. Differences in occupational status or perceived social support were not related to affect. However, at follow-up, greater affective disturbance was related to a higher number of clinical exacerbations between baseline and follow-up.

No change over time (i.e., 6 months) was found with respect to pathology,

attention, memory, or affect. This lack of progression was likely due to the fact that these subjects were still early in the disease process and the time interval was not sufficient to document change. The fact that executive functioning appeared to improve over time was likely due to the fact that different measures were used to assess executive functioning at baseline and follow-up, and the fact that a regression toward the mean may have taken place.

The lack of significant relationship between active lesion load and the outcome measures was attributed to three possible reasons. First, this measurement did not reflect the surface area of the lesions. Second, the measurement did not reflect the totality of brain damage (i.e., active, as well as old, lesions). Third, given the early stages of the disease process in these individuals, it is possible that neurons were still spared (i.e., grey matter preserved).

Finally, the test-retest reliability of the measures was established, and the statistical power of the correlations reported was calculated. Power was less than ideal, despite the very large effect sizes that were documented.

The limitations and strengths of this study, as well as the implications for future research were discussed.

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VITA AUCTORIS

Lisa Smith-Walker (née Smith) was born on May 24, 1968, to Laurence and Judy (née Jolliffe) Smith, in Oakville, Ontario. She was graduated from Nelson High School, in Burlington, Ontario, in June of 1986, when she received an Ontario Scholarship. From 1986 to 1990 she was enrolled as an undergraduate student at Queen's University at Kingston, Ontario. She was conferred the first class degree of Bachelor of Science with Honours in Psychology, in June of 1990. From 1990 to the present day she has been enrolled as a graduate student at the University of Windsor, Windsor, Ontario, where she has been awarded two University of Windsor Postgraduate Tuition Scholarships and three Ontario Graduate Scholarships. She was conferred the degree of Master of Arts in Psychology in October of 1992. She completed a practicum with the Lester B. Pearson Centre for Children and Youth, of Chatham, Ontario, in 1991, and an internship with the Ottawa General Hospital, of Ottawa, Ontario, in 1994. She is currently a doctoral candidate for the Doctor of Philosophy degree in Clinical Neuropsychology at the University of Windsor and hopes to graduate in Spring 1998.